S. HRG. 103–302

NAS COMMITTEE REPORT ON AGENT ORANGE

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NAS Committee Report on Agent Orang...

HEARING

BEFORE THE

COMMITTEE ON VETERANS' AFFAIRS
UNITED STATES SENATE

ONE HUNDRED THIRD CONGRESS

FIRST SESSION

JULY 27, 1993

Printed for the use of the Committee on Veterans' Affairs

MAY 4 1994

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NAS COMMITTEE REPORT ON AGENT ORANGE

TUESDAY, JULY 27, 1993

U.S. SENATE,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, DC.

The Committee met, pursuant to notice, at 11:18 a.m., in room DG–50, Dirksen Senate Office Building, Hon. John D. Rockefeller IV (Chairman of the Committee) presiding.

Present: Senators Rockefeller, Akaka, Daschle, and Campbell.

OPENING STATEMENT OF CHAIRMAN ROCKEFELLER

Chairman ROCKEFELLER. I apologize to the witnesses and to all. To our Secretary, I apologize for our delay in getting started. We just had a series of four or five votes, and they all fell one right after the other.

I'm afraid also, since this is a day of conferences all over this building, that the rest of the hearing may also be thrown into some form of turmoil. We have an extremely important meeting about the deficit reduction bill today from 12:15 p.m. to 2:15 p.m., which Senator Daschle is to chair, so to speak. I've consulted with Senator Daschle and other Members of the Committee about how to accommodate Senators' schedules and the availability of our witnesses. This is very difficult and awkward, so we've decided to proceed in the following manner:

Following our opening statements, we'll hear the testimony of the National Academy of Sciences, and then we'll proceed directly to Secretary Jesse Brown's prepared statement. Following that, we'll go back to NAS for some questions. We'll suspend the hearing at 12:15 p.m. We will then pick up at 2:15 p.m. where we left off, with questions to both NAS, if we're not finished with them, and to the Secretary—that is, depending on whether or not the Secretary can be here. I simply don't know, and I apologize again to the Secretary. I expect the hearing to conclude sometime before 4 p.m. I'm sorry that we have to do it this way, but these are crazy days.

I thank the witnesses, I thank the press, I thank all who are here today for their patience and for their understanding.

Now, I welcome you to this hearing. This is a red-letter day in the effort to resolve the Agent Orange issue. We will focus on a report released this morning by the National Academy of Sciences. For the first time, an independent review of the scientific evidence shows that there is a clear association between Agent Orange exposure and five diseases. It further shows that there is a likely relationship between exposure and several additional diseases. Finally,

the report indicates that for numerous other conditions, including reproductive and neurological effects, there is inadequate information to conclude a definite association—that is to say, there may be an association, but we simply do not have complete information.

These are incredibly important findings. Contrary to what the Federal Government has said over the years, the report also suggests that further epidemiological studies are possible and should be done, and done now. This is enormously encouraging.

NAS conducted an 18-month review under the Agent Orange Act of 1991—and I'll have something to say about one of its authors in a moment—a law that originated in our Committee. The report is thorough, the report is well balanced, the report is scientifically impressive. It will be extremely useful to those of us in Congress and to the VA.

This has been a very emotional subject for a long time. I think we have hope now that the mystery surrounding Agent Orange can indeed be solved. I plan to hold a followup hearing in September, after those interested in this issue have had a chance to very carefully review the NAS report.

Now I come to what I feel just as good about, and that is to say that I choose to, want to, am proud to, and have looked forward to passing the gavel on this day to my colleague, Tom Daschle of South Dakota, for this hearing. This is a symbolic act, this is a substantive act, this is a deserved act; this is an act of great emotional importance, I think, to both of us.

Since his day as a Member of the House, Tom has been the strong national leader on the issue of Agent Orange. He was one of the key authors of the law that made this report possible, the Agent Orange Act of 1991. He has worked tirelessly, fervently, and with the professional and service background that adds the extra dimension of tenacity and ferocity that is needed in Congress to drive things through. His experience, what he has seen with others, and what he feels in his own soul, are what drive Tom Daschle on this subject, as well as his sense of justice and fair play and doing what is right.

Tom, I thank you for your tireless work in this area, for your overwhelming contribution in getting us to this point. Our Nation's veterans appreciate your leadership and I know they are better off today because Senator Tom Daschle of South Dakota has helped this day to come. So I pass the gavel—it is symbolic and although this is the kind of thing one is usually embarrassed to do, I'm not embarrassed to do it, I'm proud to do it—to Tom Daschle of South Dakota.

[The prepared statement of Chairman Rockefeller appears on p. 23.]

OPENING STATEMENT OF SENATOR DASCHLE

Senator DASCHLE [presiding]. Jay, thank you very much for your generous words and for giving me that responsibility this morning. I'm very grateful and profoundly appreciative to you not only for this day, but for the incredible support that you've shown us in this effort for so many years. You've been by our side, you've been part of this effort. You have given us the kind of strength that we have

needed to be successful, and were it not for that kind of support, we wouldn't be here today.

So I am grateful to you as a friend, as a fellow Senator, and now as our Chairman, that because of that leadership and commitment we are able to come to this point. So I appreciate it more than I can express. Thank you.

Chairman ROCKEFELLER. Thank you, Mr. Chairman.

Senator DASCHLE. For many of us in this room and for the thousands unable to be here, it has been a long, difficult struggle, as Senator Rockefeller just indicated. Vietnam veterans have been subjected to many indignities. Like those who fought before and after them, they faced the horrors of war. Unlike others, too often they faced an unappreciative public upon their return home.

As we all know, they faced enemies they had hoped were their friends—Agent Orange and other herbicides used as defoliants in the war. But many Vietnam veterans will tell you that their greatest indignity has been suffered at the hands of the Government that sprayed those herbicides and, for so many years, avoided responsibility for the consequences of that decision. Today I am encouraged that the process put in place to help us begin taking that responsibility is at long last working. I have not been able to say that with confidence before.

Although the process that we began through the Agent Orange Act of 1991 is just the beginning, the quality and comprehensiveness of the report being released today by the National Academy of Sciences suggests to me that, for the first time, veterans and the American public have a solid reason to believe that their concerns about exposure to Agent Orange, dioxin, and other toxic chemicals are at long last being taken seriously by people in a position to help address those concerns.

The NAS report on the possible health effects of exposure to Agent Orange and other herbicides used in Vietnam is essentially a baseline reading, with five followup reports to come over the next 10 years as additional scientific evidence is developed. It answers some of our questions related to specific disease outcomes, and recommends further research that may shed light on those issues. It should put to rest the chants of those who have claimed that "Agent Orange never hurt anybody" or "We'll never be able to answer those questions."

The American people owe a great deal of gratitude to the 16 scientists who, over the past 18 months, without compensation—let me emphasize this—without compensation, immersed themselves in the scientific literature related to the health effects of Agent Orange and navigated the political and emotional waters surrounding this debate. It is certainly a thankless job, but I want each of them to know that I and many others today publicly acknowledge that effort and thank them. It is clear to me from my review of the report that they have done what Congress asked with a high degree of professionalism and, even more importantly, that they understand the significance of this effort. I also want to thank the NAS staff for their support in this undertaking.

These scientific reports are valuable and important in their own right as a state-of-the-art measure of the state of the science. I want there to be no misunderstanding about that. The Agent Or-

ange Act of 1991, however, requires that the Secretary of Veterans Affairs use this report and any other relevant scientific or medical information to determine which, if any, of veterans' illnesses should be service-connected for disability compensation purposes. Secretary Brown has a history of concern about this issue, and he has already assured us that he wants to do everything possible to ensure that Agent Orange victims are given the compensation they deserve as soon as the science can point us in the right direction.

In addition to hearing from the National Academy of Sciences on where the science has taken us so far and what further study may be necessary, the Committee looks forward to hearing Secretary Brown's view of where we go from here in terms of policy.

Again, let me express to all of those responsible for this day my deep appreciation. I speak, I'm sure, on behalf of the thousands of Vietnam veterans who have waited for the truth to be known and for us, as a government, to deal with the truth.

[The prepared statement of Senator Daschle appears on p. 23.]

Senator DASCHLE. With that, let me begin by introducing our first panel: Dr. Harold Fallon, the Chairman of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, accompanied by David Kriebel, a committee member; and Dr. Kenneth Shine, the President of the Institute of Medicine at the National Academy of Sciences. Dr. David Tollerud, the Vice Chairman, is welcome to join us at the table. I see he's not there, but he's certainly welcome if and when he arrives.

Gentlemen, again, let me thank you for being here, and we look forward to your testimony at this time.

STATEMENTS OF DR. KENNETH I. SHINE, PRESIDENT, INSTITUTE OF MEDICINE, NATIONAL ACADEMY OF SCIENCES AND DR. HAROLD FALLON, CHAIRMAN, INSTITUTE OF MEDICINE'S COMMITTEE TO REVIEW THE HEALTH EFFECTS IN VIETNAM VETERANS OF EXPOSURE TO HERBICIDES, ACCOMPANIED BY DR. DAVID TOLLERUD, VICE CHAIRMAN, IOM COMMITTEE; DR. DAVID KREIBEL, DR. KATHY RODGERS, AND DR. JESSE BERLIN, IOM COMMITTEE MEMBERS

Dr. SHINE. Mr. Chairman, Members of the Committee, I'm Kenneth Shine, the President of the Institute of Medicine. I'm pleased to have the opportunity to testify before the Senate Committee on Veterans' Affairs on the Institute of Medicine's report prepared by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. I will provide a brief summary of the background on the committee's report and the Institute of Medicine. The chairman of the committee, Harold Fallon, will present a brief overview of the committee's findings and recommendations, and David Kriebel, a member of the Committee, is prepared to answer additional questions.

In response to decades of concern surrounding the possible long-term health consequences of exposures to herbicides and the contaminant dioxin, Congress—this Committee—directed the Secretary of Veterans Affairs in Public Law 102–4, signed on February 6, 1991, to request the National Academy of Sciences to conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health effects of exposure to

Agent Orange and other herbicides used during the Vietnam conflict.

The report from the Institute of Medicine's Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, entitled "Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam," reviews and evaluates the available scientific evidence regarding the association between exposure to dioxin or other chemical compounds and herbicides used in Vietnam and a wide variety of health effects, and provides the committee's best assessment of this body of knowledge for the Secretary of Veterans Affairs to consider as the Department exercises its responsibilities to Vietnam veterans.

The report also describes areas in which the available scientific data are insufficient to determine whether an association exists, and provides the committee's recommendations for areas in which future research is likely to be most productive.

The National Academy of Sciences was created by an act of Congress and signed into law by President Lincoln in 1863 and is dedicated to the furtherance of science and technology, and to their use for the promotion of the general public welfare. The Institute of Medicine was chartered by the National Academy of Sciences in 1970 to serve as an advisor to the Federal Government on issues that affect the public's health, as well as to act independently in identifying important issues of medical care, research, and education. The Institute of Medicine brings to this mission more than two decades of experience in conducting independent analyses of pressing health problems that involve Federal policy decisions.

As you pointed out, Mr. Chairman, the Committee to Review the Health Effects in Vietnam Veterans included 16 members, representing a wide range of expertise. The members voluntarily participated on the committee and, as you noted, served without compensation. Their report is a unanimous consensus report. The committee was chaired by Harold Fallon, M.D., Dean of the School of Medicine at the University of Alabama, Birmingham. David Tollerud, M.D., M.P.H., Director of Occupational and Environmental Medicine at the University of Pittsburgh, served as Vice Chair. Norman Breslow, Professor of the Department of Biostatistics at the University of Washington, was the committee liaison with the Institute of Medicine Board on Health Promotion and Disease Prevention, which was responsible for overseeing the study.

All the committee members were selected because they are leading authorities in their scientific fields, are well respected by their colleagues and peers, have no conflicts of interest with regard to the matters under study, and indeed have taken no public positions concerning the potential health effects of herbicides in Vietnam veterans or related aspects of herbicide or dioxin exposure. The committee thus has provided a fresh analysis of the issue, which is both scientifically complex and emotionally charged. This report reflects the committee's unanimous thorough and unbiased scientific judgments.

As with all of the reports from the Institute of Medicine, the committee's work was also reviewed by an independent panel of experts to whom the committee had to respond.

I would now like to ask Dr. Fallon to provide an overview of the report.

[The prepared statement of Dr. Shine appears on p. 25.]

Senator DASCHLE. Dr. Shine, if you could just allow me to interrupt for a moment, I obviously have shown my lack of experience as Chairman of this Committee, because I failed to call upon my colleagues for their opening remarks, and I would like to do so at this time, if I could.

I deeply appreciate the fact that they're here, and let me call on my friend, the Senator from Hawaii, Senator Akaka, for his opening comment, and then I will call on Senator Nighthorse Campbell for his.

OPENING STATEMENT OF SENATOR AKAKA

Senator AKAKA. Thank you, and good morning, Mr. Chairman. I'd like to join you in welcoming our panels—Secretary Brown, Dr. Fallon, Dr. Shine, and Dr. Kriebel—and other officials from VA and the National Academy of Sciences who are here to discuss the Academy's first report on the health effects of herbicides used in Vietnam, including Agent Orange.

I want to say especially greetings to Dr. Shine. I spent the last weekend with him at Woods Hole. I certainly enjoyed it, and he chaired one of the sessions there.

I also want to associate myself, Mr. Chairman, with the remarks made by Chairman Rockefeller about your efforts over a period of time on Agent Orange, and I certainly share his remarks that he made about you and what you've done with this issue.

The controversy over Agent Orange has been a painful one for Vietnam veterans as well as for those of us involved in developing veterans policy. The release of today's NAS report hopefully marks, if not an end, at least a beginning of an end to this national controversy.

Mr. Chairman, based on the report's findings, I believe VA should add Hodgkin's disease and PCT to the list of presumptively service-connected conditions and to seriously consider adding respiratory cancers, prostate cancer, and multiple myeloma to the list. The NAS report's extensive recommendations for improving research on herbicide exposure should also be seriously considered.

Mr. Chairman, I should note that NAS' initial report is both good news and bad news. The bad news is that there is no longer any doubt that many serious diseases are in fact related to herbicide contact and that, as time goes by and latent diseases manifest themselves, we are probably going to see more diseases associated with exposure to defoliants used in Vietnam. The good news, if we can call it that, is that the report validates the presumptive policy toward the Agent Orange issue embodied in Public Law 102–4, the Agent Orange Act of 1991.

No one deserves greater credit for this policy than you, Mr. Chairman—Tom—and our colleague John Kerry. Through sheer force of will, you impelled VA to make an about-face on this issue and led the fight in Congress that two years ago resulted in the requirement for the NAS study itself, as well as in the codification of nonHodgkin's lymphoma, soft-tissue sarcoma, and chloracne as service-connected conditions. The report that is the subject of to-

day's hearing is a tribute to your diligence, Mr. Chairman, your compassion, and your foresight on this issue.

If there is an object lesson here, it is that veterans should always be accorded the benefit of the doubt. If we had listened to their pleas for help from the beginning, we could have avoided years of anguish. But that is well in the past. We must now apply our experience with Agent Orange, both political and scientific, to the needs of other veterans who are in pain, such as Persian Gulf veterans who may have been exposed to environmental toxins during that conflict.

Thank you, Mr. Chairman, for giving me the time to make this statement, and I look forward to reviewing the testimony of our witnesses.

[The prepared statement of Senator Akaka appears on p. 24.]

Senator DASCHLE. Danny, thank you for an excellent statement and for your kind words. I appreciate it very much. As I indicated earlier, our success, in large measure, has been based upon the support that we've enjoyed from colleagues like you, and I'm very grateful to you for the support you've shown for many, many years on this issue. I know that support will continue as we go through the challenging years ahead.

Let me at this time call upon our colleague Ben Nighthorse Campbell for any opening remarks he might make.

OPENING STATEMENT OF SENATOR CAMPBELL

Senator CAMPBELL. Thank you, Mr. Chairman. I would like to introduce a written statement for the record and make a very brief comment. Personally, I'd rather hear Dr. Shine talk than listen to myself. But I do appreciate this hearing taking place.

I guess one of the problems I've had, like many other veterans have, is that we're so quick to forget soldiers once they're out or once the battles are over, and I guess I've always increased the problem by realizing that we asked them to go in under very difficult circumstances. It's bad enough to ask them to face visible enemies, but when they have to sometimes face enemies within in a jungle where they have little understanding of the effects of what our own side is doing and then come home to a country that in many cases talks about normalization and not enough about the missing in action, it adds insult to injury.

I am not a doctor and don't pretend to know very much about the different diseases that have been attributed to Agent Orange, but I can tell you one thing: Any chemical that can kill trees has got to have some damaging effect on human beings, too. Over the years of pouring 19 million gallons out over an area where our own troops were, there's no question in my mind that we really owe a major effort to trying to make sure that the people that were affected are taken care of and the families of the people that were affected are compensated. I'm certainly supportive of anything we can do in that direction.

I know it's quick now on the part of a lot of us to say, "Well, we're in a budget deficit. We don't have much money. We've got to balance the budget," but I think these veterans have paid their dues and paid their portion of a commitment that we certainly need to move forward on it.

Thank you for this Committee hearing.

[The prepared statement of Senator Campbell appears on page 25.]

Senator DASCHLE. Thank you very much, Ben, for your comments. I couldn't agree more. We are quick to send them, we're just not so quick to provide them with the care once they come back.

Senator DASCHLE. Dr. Fallon, welcome, and thank you for coming.

Dr. FALLON. Thank you. Mr. Chairman and Members of the Committee, I am pleased to have the opportunity to testify before the Senate Committee on Veterans' Affairs on the Institute of Medicine's report prepared by our Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. I will provide a brief overview of the committee's findings and recommendations.

A bitter legacy of the Vietnam War has been the decades of concern over the health effects of Agent Orange and other herbicides. More than 19 million gallons of herbicides were sprayed over South Vietnam in the years between 1962 and 1971, before reports of health effects in laboratory animals ended herbicide spraying. Most large-scale spraying took place from the air, but a considerable amount of spraying was also done from boats and ground vehicles and by soldiers carrying back-mounted equipment.

Since that time, some of the three million Americans who served in or near Vietnam have come to suspect that their wartime exposure to herbicides caused them to develop cancer or their children to have birth defects. This concern has helped initiate literally thousands of scientific studies on the health effects of herbicides and of dioxin, which contaminated about two-thirds of the herbicides used in Vietnam, yet the issue remains shrouded in controversy and mistrust.

This issue has been a source of great anguish for Veterans, for their families, and for the Nation at large. Vietnam veterans made great personal sacrifices in serving their country, yet they have faced continuing uncertainty about whether exposure to the herbicides has led to past health problems or could lead to problems in the future. Some of these veterans and their families feel that their pain and suffering has been ignored and that these questions have not been adequately addressed.

Recognizing this uncertainty, the U.S. Congress passed the Agent Orange Act of 1991. That legislation asked the National Academy of Sciences to do a comprehensive review and evaluation of the available scientific and medical evidence regarding this issue. The task was undertaken by the committee under the Institute of Medicine, and today our committee is releasing its report.

To gather information for the report, the committee held three public meetings to allow veterans and other interested individuals to voice their concerns and opinions. In addition, members of the Committee and staff sought and received information from a broad array of individuals and organizations, including veterans groups, congressional committees, Federal agencies, scientific experts, and the public. This wide-ranging dialog contributed substantially to the report.

We studied both the toxicological and epidemiologic data on herbicide exposure. After reviewing thousands of studies—over 6,000—

we focused on approximately 230 epidemiologic investigations for detailed review and analysis. It's important to note that most of these studies did not involve Vietnam veterans. Rather, they were studies of people who were exposed to herbicides as a result of their jobs or as a result of contact in the environment—for example, because of a nearby industrial accident. These types of exposures often were high and for long periods of time.

Getting a clear picture of the health risks for Vietnam veterans is not so straightforward, because the levels of exposure were wide ranging. Indeed, while most veterans probably had lower exposures, some may have experienced levels as high as those with occupational or agricultural exposures. What is uncertain is how many veterans may have been exposed to the higher levels and who these individuals are.

Based on the evaluation of the studies reviewed, our committee found sufficient evidence of a statistical association between exposure to herbicides or dioxin and three types of cancer—soft-tissue sarcomas, nonHodgkin's lymphoma, and Hodgkin's disease. We also found sufficient evidence of an association with two skin diseases—chloracne and porphyria cutanea tarda, or PCT. We found limited or suggested evidence of an association between exposure to the herbicides used in Vietnam and three other types of cancer—respiratory cancers, prostate cancer, and multiple myeloma.

For most of the other cancers, diseases, and disorders reviewed by the committee, the scientific data were not sufficient to determine whether an association exists. This includes such cancers as bone cancers and leukemia and disorders ranging from birth defects to nervous system disorders. However, for a small group of cancers, including gastrointestinal cancers and brain tumors, the committee found limited or suggestive evidence to conclude that there is no association between these cancers and herbicide exposure.

The greatest problem that we encountered in our study was a severe lack of information about the exposure of individual Vietnam veterans to herbicides. Except for particular groups, such as the individuals directly involved in spraying operations, information on the extent of herbicide exposure among veterans is practically nonexistent.

New biochemical techniques can detect low levels of dioxin in the blood, but we did not find these measures are useful for arriving at individual exposures. People metabolize dioxin at different rates, and almost all Americans have some background exposure to dioxin; therefore, they will have detectable serum levels of dioxin. Furthermore, not all of the herbicides used in Vietnam contained dioxin. Approximately one-third did not.

This lack of data is why we are compelled to focus largely on epidemiologic studies of groups other than Vietnam veterans. We simply do not know enough about the exposure of veterans to determine what degree they were or are at risk.

We do feel, however, that it is possible to develop better methods of determining exposures amongst individual veterans. Rather than relying on measures of dioxin in the blood, we recommend that exposure evaluations draw on historical reconstruction. These reconstructions take into account such factors as troop movements,

ground and perimeter spraying, herbicide shipments to various military bases, the type of terrain and foliage typical of the locations sprayed, and the military mission of the troops located there.

Historical reconstructions require substantial professional judgment; therefore, the committee further recommends that a nongovernmental organization be commissioned to develop and test models of herbicide exposure for use in future studies of Vietnam veterans. These exposure models should, in turn, be evaluated by an independent scientific panel to determine their usefulness. The independence of these scientific groups should allay the public's concern about impartiality and scientific credibility.

If a better model of exposure can be developed, a number of important epidemiologic studies become possible. Highest priority should be given to those studies that could change the balance of evidence for or against an individual health effect. Research on reproductive effects should also receive high priority.

In addition, our committee recommends that the study of the Ranch Hand cohort, which has been looking at individuals involved in the Air Force's spraying program, be continued and expanded. A similar study should look at the members of the Army Chemical Corps and an appropriate comparison group. Both the Ranch Hand and Chemical Corps veterans are known to have had significant exposure to herbicides.

Our committee was not asked to make judgments regarding individual injuries or the appropriate compensation for Vietnam veterans, and we did not do so. Rather, we were asked to provide information that the Secretary of Veterans Affairs could use in exercising the responsibility of the Department of Veterans Affairs to Vietnam veterans.

Over the years, extreme views have evolved over this issue. On one extreme is the view that Agent Orange and dioxin caused a wide range of disease; on the other is the suggestion that exposure to Agent Orange has not led to health problems. Our committee has determined through an extensive review of the scientific literature that indeed there does appear to be a link between exposure and certain diseases.

We believe that our report is a comprehensive, unbiased scientific review of the available evidence concerning this issue. This report will not end the controversy, but we hope that it will provide an agreed-upon base of information from which we can proceed to answer the questions that remain.

I would like to submit the Executive Summary of the committee's report for the record, and I would also like to acknowledge the extraordinary assistance of Dr. Michael Stoto and the staff of the Institute of Medicine in preparing our final report. Their help was invaluable.

My colleagues and I are prepared to respond to any questions that you and other Members of the Committee may have. Thank you.

[The prepared statement of Dr. Fallon appears on p. 26.]

Senator DASCHLE. Dr. Fallon, thank you for a very thorough statement, and without objection, the Executive Summary of the report will be made part of the record at this time.

[The Executive Summary referred is retained in the Committee files.]

Senator DASCHLE. As indicated by our Chairman, Senator Rockefeller, if you find it to be agreeable, I think we will excuse this panel so we can hear the testimony now of our Secretary of Veterans Affairs. I thank you for your statements and your presence, and we will see you early this afternoon.

Senator DASCHLE. With that, let me call to the table Secretary of Veterans Affairs Jesse Brown for his testimony. As I understand it, he has a number of people who are accompanying him: Mary Lou Keener, General Counsel; John Thompson, Assistant General Counsel; R.J. Vogel, Deputy Under Secretary for Benefits; J. Gary Hickman, Director of Compensation and Pension Service; and Susan Mather, Assistant Chief Medical Director, Environmental Medicine and Public Health.

We are pleased that you could be with us, and we appreciate, again, your tolerance of this schedule and your patience. We are grateful to you for coming and for giving us the time that you have, Secretary Brown, and we look forward to your testimony.

STATEMENT OF HON. JESSE BROWN, SECRETARY OF VETERANS AFFAIRS, ACCOMPANIED BY MARY LOU KEENER, GENERAL COUNSEL; JOHN THOMPSON, ASSISTANT GENERAL COUNSEL; R.J. VOGEL, DEPUTY UNDER SECRETARY FOR BENEFITS; J. GARY HICKMAN, DIRECTOR, COMPENSATION AND PENSION SERVICE; AND DR. SUSAN MATHER, ASSISTANT CHIEF MEDICAL DIRECTOR, ENVIRONMENTAL MEDICINE AND PUBLIC HEALTH

Secretary BROWN. Thank you very much, Mr. Chairman. Mr. Chairman, I would like to begin by expressing the appreciation of the veterans' community and my personal admiration for the leadership you and this Committee have shown in addressing this difficult issue. We're here today, Mr. Chairman, in part because of you, and for that, sir, I thank you very, very much.

Today's hearing marks a milestone in the search for truth about Agent Orange. Since 1978, when the issue first surfaced, Vietnam veterans and their families have been waiting for answers to their many questions about Agent Orange. As a member of a veterans' service organization, I was aware of the fears and the frustrations of my fellow Vietnam veterans. As Secretary of Veterans Affairs, I am committed to taking a fresh look at the issue and to do the right thing. Vietnam veterans deserve no less.

As you know, one of the principal sources of frustration has been the inability of the scientific community to provide us with definitive answers about the health effects of exposure to Agent Orange. The conclusions reached in the scientific research were often conflicting and confusing. Every side of the controversy could point to some study to support their position. As the controversy dragged on, positions hardened and the dialog became impassioned and emotional.

It was at least partially in response to this stalemate that Congress mandated VA to contract with the National Academy of Sciences to perform an unbiased review of the scientific literature and to offer its assessment. I must acknowledge the task was not

an easy one for the Academy. We are now reviewing their report and will, within the time frame mandated by the Agent Orange Act of 1991, make the necessary decisions.

There are some decisions, however, that need not wait the full 60 days that the Congress gave us in that law. I am prepared to act right now on some of the Academy's recommendations. I'm referring to those conditions for which they found scientific evidence sufficient to conclude that there is a positive association between exposure to an herbicide agent in Vietnam and some diseases. I have directed the Veterans Benefits Administration to begin the rulemaking process to recognize Hodgkin's disease and porphyria cutanea tarda, also known as PCT, as being associated with exposure to herbicides used in Vietnam.

We do not need to take any actions on soft-tissue sarcoma and chloracne, since the VA already recognized these as being associated with exposure. VA's rule regarding nonHodgkin's lymphoma will be revised to reflect its association with herbicide exposure.

I have also directed the Veterans Benefits Administration to identify Vietnam veterans on the Agent Orange register who suffer from these five diseases. We will contact those who have not filed claims for compensation to urge them to apply. I have also asked the service organizations to assist in this outreach effort.

I believe this prompt action is appropriate, indeed, mandatory. I am not prepared today, however, to render judgment about the Academy's report as it relates to other conditions. It is imperative, in my view, to fully analyze the implications of this report, and to expeditiously act on the recommendations from that review.

I, therefore, have established an internal, high-level panel to review the report and to solicit comments on it from other medical and scientific authorities, representatives of veterans' service organizations, and other interested parties. Dr. Susan Mather, VA's Assistant Chief Medical Director for Environmental Medicine and Public Health, will chair this panel. Membership will include top-ranking officials of the Veterans Health Administration, the Veterans Benefits Administration, and General Counsel. The panel will advise me of their findings in time for me to make decisions within the 60-day time period.

I am also acting now to accept key recommendations of the Academy with respect to future research. I'm keenly aware that Vietnam veterans have been waiting too long, and too often have been told to wait for more research. I am, however, persuaded by the Academy that more research is needed if we are to put this issue behind us.

I think the recommendations of the Academy are well presented, and they appear to be soundly based. I have, therefore, asked the Under Secretary for Health to prepare an action plan that will implement the research recommendations in a timely manner. I would like to comment about several of the recommendations.

Perhaps the fourth recommendation is the most important. The Academy recommended exploring the feasibility of developing a method for historical herbicide exposure reconstruction for Vietnam veterans. I have accepted this recommendation. There are many conditions for which the Academy was unable to give definitive recommendations. In large measure, this was due to inadequacy in

the scientific literature, particularly with respect to verified exposure.

If a method for determining exposure with greater certainty can be devised, we will be able to better focus our research and arrive at more supportable conclusions. Indeed, this may serve as a way to answer whether Vietnam veterans are at risk for adverse health due to Agent Orange exposure. Because of its potential importance, I have asked that this be given high priority for implementation.

The Academy also recommended that the Air Force Ranch Hand study be continued, with an external review by an independent, nongovernmental scientific panel. I have written to the Acting Secretary of the Air Force to urge serious consideration of this proposal.

The Academy additionally recommended that members of the Army Chemical Corps and an appropriate comparison group be followed in a study similar to the Ranch Hand study and have oversight from an independent, nongovernmental scientific panel. VA recently conducted a mortality and morbidity study of Chemical Corps personnel who served in Vietnam. The study's results were reported on this group in 1990. No unusual findings were noted at that time. VA researchers are currently working to expand the study to include Army Vietnam-era veterans with chemical occupation specialties who did not serve in Vietnam. The Department will seek to have this research project reviewed by outside experts to determine if improvements can be made, and we will submit the results to the independent panel for their review.

The Academy recommended that military personnel records be modified to include a marker for Vietnam service. We agree. VA will explore the feasibility of accomplishing this. It will require a coordinated effort between several departments and agencies.

I want to assure you and the Vietnam veterans community that I am approaching this issue with an open mind. In those areas where I believe the Academy has made definitive findings, I have acted to implement them. As to the remaining areas, I will take the time provided by statute to satisfy myself that the action of the Department is the right action and that it puts veterans first.

I also want to note that I intend to pursue further discussion of this issue with Members of this Committee and the House Committee on Veterans' Affairs. I am certain that working together we can achieve a just resolution.

Mr. Chairman, I know that everyone will not be satisfied; however, I deeply hope that our actions and our intentions will allay the doubts of many who, hopefully, will acknowledge that a good faith effort is being taken toward addressing this issue and their concerns.

Mr. Chairman, that concludes my prepared statement.

[The prepared statement of Secretary Brown appears on p. 28.]

Senator DASCHLE. Secretary Brown, thank you for a very fine statement and for the action that you've announced this morning. We commend the VA for their quick action on the first category, and I, like you, feel that additional review is essential to continuing the work to establish the necessary data for us to make enlightened decisions in future years. So I certainly find the VA's actions thus far to be encouraging, and I'm hopeful that as we continue to

work together we can find ways with which to ensure that we resolve the outstanding questions.

We have a couple of minutes, and I would like to begin, if I could do so, by asking a couple of questions, and perhaps we might even be able to get through the questions that I had originally planned.

Public Law 102–4 requires the Secretary to determine, based upon the NAS report and any other relevant scientific and medical information he chooses, which, if any, disease outcomes in humans—the law doesn't say veterans—have a positive association with exposure to herbicides used in Vietnam, and provide presumptive disability compensation for those disabilities related to those disease outcomes. As you know, the test in the law for positive association is whether "the credible evidence for the association is equal to or outweighs the credible evidence against the association."

Let me ask, based upon that understanding, how you made your determination with respect to this mandate and how you will make determinations for the remaining categories.

Secretary BROWN. Well, I think the disabilities listed in category A clearly meet the test and the language that's described in law. However, we want to take a closer look at categories 2, 3, and 4 to make sure that we take into consideration all available evidence and that our decision is in accord with the congressional mandate.

Senator DASCHLE. Could you envision making distinctions between diseases in the same category?

Secretary BROWN. I would hesitate to make a statement to that effect at this particular time, Mr. Chairman. I'm going to wait until we've had a chance to take a close look at the entire report, and, of course, we will be looking at each and every disease, as mandated in the law. But at the same time, exactly how we're going to approach it will be determined based upon our analysis of the report itself.

Senator DASCHLE. As you know, the Agent Orange Act explicitly requires the VA's initial contract with NAS to provide for followup scientific reviews and reports for 10 years after the first NAS report is issued, which is, of course, today. What does the contract between the VA and the NAS say about followup reviews?

Dr. MATHER. We are going on with that review and are working on the contract for the next report.

Senator DASCHLE. Does the contract specifically require followup reviews?

Secretary BROWN. Mr. Chairman, we'll get a response for the record on that question.

Senator DASCHLE. OK. As I understand it, there is no provision in the contract, and I would be interested in knowing why there isn't. So not only do I want to know about your understanding of the contract itself, but I'd like to know why the contract doesn't explicitly require followup reviews.

Could you also provide—perhaps Mary Lou would be the best one to do this—the Committee with a legal opinion supporting the interpretation of the contract process and the reviews to be followed? That would be very helpful in creating the legislative history.

Do you intend to enter into another contract with NAS that would fulfill the requirements under the act?

Secretary BROWN. We will make that decision once we've had an opportunity to look at the entire situation, and within the 60 days.

Senator DASCHLE. Is there any reason to believe that you would decide not to enter into another contract?

Secretary BROWN. At this point, no, there is no reason to believe we would not enter into another contract.

Senator DASCHLE. Based upon the report, what action do you anticipate taking with respect to the blood and tissue testing in the archive programs addressed in the Agent Orange Act?

Secretary BROWN. Well, here again—as you know, in the report itself, they gave little weight to maintaining an archive on blood and tissue. Here again, I think we will make a decision on whether or not we will accept that recommendation or continue to move forward as we have been.

Senator DASCHLE. I would appreciate in this case especially that you share whatever information that you develop as you go along, and certainly your ultimate decision, with the Committee just as soon as you can, Secretary Brown.

Secretary BROWN. We will, sir.

Senator DASCHLE. Most of the scientific studies the committee reviewed focused on exposure to herbicides in the workplace and industrial accidents and on farms, not on exposure to Agent Orange in Vietnam, as you know. As part of the effort to facilitate research on veterans, the committee strongly recommended the establishment of a computerized registry for all veterans who served in Vietnam, or "flagging" for Vietnam service in DOD and VA records. I'd like to ask if you view this to be a practical way of addressing the need to follow veterans exposed to Agent Orange. Can it be done? How long would it take? What do you think it might cost?

Secretary BROWN. Let me say I do agree that it is needed. I think it is very important, and we see a justification coming out of this process. As I mentioned in my opening statement, our Agent Orange register contains over 2,000 names, and we are going to be able to pull out, based on diagnostic codes, those individuals who are suffering from one of the five diseases that now have been clearly identified or associated with exposure. We're going to be writing directly to those individuals, inviting them to file a claim for disability compensation. So that's a good example of why we need to keep track of these veterans, because this is clearly a process that continues to evolve.

We're looking for other ways to verify exposure. We're looking at identifying new biomarkers. We have one that's primarily based on blood where we try to identify the agent 2378–TCDD. It is my understanding, based on the report, that the Academy feels we need to look at some biomarker in the DNA structure. We agree with that, and we want to move forward. This is an emerging technology, and we welcome anything we can use to be able to understand what we're up against, and do the right thing by veterans.

Senator DASCHLE. Secretary Brown, you can forgive those veterans who may remain very skeptical about the VA response. They've been subjected to an extraordinary amount of bureaucratic intransigence for so long, unresponsiveness, fighting veterans all along the way—12, 13, 15 years, in some cases. What can you tell them

this morning that will make them more confident that we've got a VA that is now responsive and that will end the intransigence?

Secretary BROWN. I would say to them—and, quite frankly, thanks to you and your effort, sir—we have to do the right thing, because when you look at the language in the law that you drafted, it makes our action very clear. We're going to follow that law. I hope out of this whole process that they see we want to be responsive, that we are making a good faith effort. We're not waiting the full 60 days to take the actions we can take right now.

There was nothing in the law saying we had to go out to the 260,000 people on our register to invite them to file claims. But here again, it shows we want to do the right thing. We want to identify those veterans who have been injured or who developed diseases as a result of having served our country and served it well. We want to identify them, and we want to make sure they receive the benefits the American people have set aside for them.

I would hope that they will give us an opportunity to look at this report very, very carefully so that when we make our decision. That decision will be in accordance with the law that has been drafted. We intend to achieve that goal.

Senator DASCHLE. We're just about out of time, and what I would like to do is to leave the record open and submit additional questions for the VA. We are almost at the point when we will have to recess the Committee. Let me ask one final question orally, and we'll reserve the rest for writing.

Have you been able to look at the recommendations regarding further research carefully enough to conclude whether or not legislation may be required with regard to fulfilling the NAS recommendations?

Secretary BROWN. No, at this point. Where we can move forward, we will do so in a way that's going to reflect the intent of Congress and our intent to do the right thing. However, I can tell you, Mr. Chairman, that if we're unable to move forward administratively, I would not hesitate to recommend to you that you initiate legislative action to remedy any deficiency we see in the process.

Senator DASCHLE. Very well. The time of 12:15 p.m. having arrived, let me recess the Committee at this point.

Let me say, Secretary Brown, because we've had this opportunity, I don't see any need for you to return this afternoon unless your people feel they have the time in their schedules. But we deeply appreciate your presence this morning and your contribution. The reaction thus far by the Department of Veterans Affairs, as I said, is encouraging, and we look forward to working with you in the weeks and months ahead.

With that, the Committee is in recess.

Secretary BROWN. Thank you, sir.

[Recess.]

Senator DASCHLE. The hearing will come to order.

Let me begin by apologizing again for yet another unexpected delay in the hearing. I had to go to an unscheduled meeting with the Majority Leader just moments ago, and it just concluded.

The panel is here, and as I understand it, Dr. Tollerud, the Vice Chairman, is with us. Dr. Kriebel is not, but we're very pleased

that all three of you could be with us this afternoon to continue in this hearing and to answer some of the questions.

I think it's important to emphasize that the purpose, of course, of these questions is to establish a hearing record so as to examine our progress both prospectively and retrospectively, and to compare that progress as we continue to make a record with the expectations laid out in the legislation and in the legislative history.

Dr. SHINE OR DR. Fallon—I don't know—Dr. Fallon will be the primary person to whom the questions will be addressed.

Dr. SHINE. I could also tell you, Mr. Chairman, that sitting to our right are two other members of the Committee, Dr. Kathy Rodgers and Dr. Jesse Berlin. They've also agreed to be present if there are some technical elements that we need to refer to them, and we will be pleased to do that.

Senator DASCHLE. Why don't we have one of the staff bring chairs, then. I think it would be good for them to be right at the table to facilitate that, should there be the need. We'll just have them join us right up there.

Let me begin, while they're bringing the chairs to the table, by saying that it's clear, certainly, from your presentation, Dr. Fallon, that your committee has taken this scientific effort very seriously and that you believe in the importance of this undertaking. Regardless of whether one agrees with every conclusion you've drawn, it's clear to this Senator that you've begun the process of addressing the underlying scientific issues that have to be addressed, and you've answered some questions and pointed us in the direction of developing answers to others.

You've done everything we've asked you to do, and I want to thank each of you for your contribution and certainly emphasize the significance of what you've done thus far. I hope that everyone here understands just how important it is, and we certainly owe you our thanks.

There's a lot of ground to cover in a somewhat limited time; therefore, it may be a requirement as a result of that limit that we submit a number of questions in writing, and I would like, if possible, to have your answers to those submitted questions within a couple of weeks.

As far as I know, none of us on the committee are scientists, at least professionally, so at the outset I just want to be sure we understand your definitions and that we're speaking the same language. When you use the term "association" in categories 2 and 3—that is, "limited suggestive evidence" and "inadequate sufficient evidence"—are you speaking of a positive association, as you say in other categories?

Dr. FALLON. Yes. Clearly, under Table 1–1 "sufficient evidence of association" is defined as evidence sufficient to conclude that there is a positive association. So when we say "association," we mean it in a positive sense, that they're correlated in the same direction.

Senator DASCHLE. Could you explain how "statistical significance" factors in here?

Dr. FALLON. I'm going to ask Dr. Tollerud to answer that one for you.

Dr. TOLLERUD. In order to put health effects under each of these categories of evidence, a large number of studies—all of the major

studies that we could find which bore on the question of a relationship between herbicide exposure and health outcome were analyzed for their statistical and scientific relevance and for various methodologic strengths and weaknesses of the studies, so that each study was assessed from a statistical standpoint, and the term "statistically significant" I think is best used when dealing with individual studies.

What we did was to evaluate those studies in total, and the placement of disease outcomes in each of these categories of evidence was a judgment by the committee members based on assembling all of that statistical information. But I think it's not possible to assign a statistical probability or a statistical value for these outcomes as they sit in the various categories.

Senator DASCHLE. Well, let me clarify your answer by asking this question. Is statistical significance understood, then, to be a part of your definition of positive association?

Dr. TOLLERUD. Yes, I think that's an accurate statement.

Senator DASCHLE. It is an accurate statement?

Dr. TOLLERUD. Yes.

Senator DASCHLE. OK. What I'm trying to get here is how you weighed the evidence and how we, as nonscientists, can understand that process for all four categories, especially the two middle categories, is defined. When a disease is in the "inadequate, insufficient evidence" category, does that mean that the evidence of the positive association is about 50/50, or does it mean that we cannot even tell that, or does it vary from disease outcome to disease outcome? Are some in that category at the 50/50 level and others at 60/40 or 40/60?

Dr. TOLLERUD. Which category are you referring to, specifically?

Senator DASCHLE. Well, the middle two categories, primarily.

Dr. TOLLERUD. I think, in general, while the committee would like to have come up with those kinds of odds or probabilities for each of the outcomes, it's simply not possible from the scientific literature to make those kinds of judgments. So I think we spent a great deal of time working out and agreeing to the wording for each of these categories, and I believe that's about as far as we can go. To use terms like "50/50" or "60/40" is not something that we can glean from the scientific literature. I don't think they're meaningful concepts scientifically.

Senator DASCHLE. Well, they're not meaningful concepts scientifically. I understand that. But they have powerful ramifications, and obviously, for those of us who are trying to understand how you arrived at a given category, that category is determined by definitions, and "positive association" is one of those definitional questions that have underlain this line of questioning. If one can't look at 50/50 or 60/40 or 40/60, could you elaborate a little bit more, then, lacking positive association, on why the middle categories were created?

Dr. FALLON. Senator, if you look at the specific definitions, we tried to write them in simple English prose to get away from scientific jargon, and I think an example of sufficient evidence for association that we give is if several small studies that are free of bias and prejudice in terms of the selection of cases show an increased risk of a certain health outcome in association with expo-

sure, then that's sufficient evidence of an association. It doesn't tell you how much the risk is. It may be a 10 percent risk, it may be a 100 percent risk. But it tells you there is an association by a series of studies that are consistent.

Under the "suggestive" category, the studies are inconsistent, so that one study might show a result that suggests the possibility of an association, but then two or three others don't show the same thing. That's inconsistent, and, therefore, it is suggestive, because there's one study, but it's by no means sufficient.

In the other category, we've lumped some that are totally inadequate because there aren't enough individuals studied or there have been no studies at all in certain areas, and insufficient in several others because although there are studies, there aren't enough patients or the study design was inappropriate.

So I think I agree with Dr. Tollerud that you can't use the kind of number percentage that we, too, would like to use, but we really can't. We can say that there's sufficient evidence of association. We can't tell you how strong the association is for each one of these. The next one, we can say there's some limited evidence. It's a high priority area to look into with new studies, but the data is just inconsistent.

Senator DASCHLE. So you've got a number of diseases for which you weigh the credible evidence for and the credible evidence against, and the law says that where it is balanced, we have a positive association. That is the criteria by which one determines a presumption of service connection, as far as the requirements of the law go. What you're saying is that in those cases for which there is not a positive association, at this point you still lack the adequate credible evidence for the association to offset what may be the credible evidence against it?

Dr. FALLON. Well, in the inadequate/insufficient category of evidence, I think most of those situations we have no credible evidence to make a decision on at all, so there isn't any balancing of positives and negatives. It's just inadequate or not there at all. There may be a few studies here and there that we have discarded because of their lack of appropriate study design.

Senator DASCHLE. Do you have any cases, Dr. Fallon, where you've truly had an example where you had approximately the same degree of credible evidence for and credible evidence against or insufficient evidence against to come out with what one would call a tie?

Dr. FALLON. Would any of the other panelists want to see if they could recall one that came out close to that?

Dr. TOLLERUD. I think part of the difficulty is that the way studies are set up and the way data are analyzed—it's sort of alluded to in this final category with "limited suggestive evidence of no association"—studies are not designed to prove that there's an association. They're designed to test the hypothesis, in a sense, that there is an association. So the statistics are all geared around the positive, and it's not—I think we would like to have what you suggested, which is credible studies showing no association, but more commonly what we have are credible—perhaps for one of these intermediate categories—a credible study that suggests an association, but it has a number of weaknesses which make it not so credi-

ble in the long run. And we have a number of other studies which may or may not show an association, but they all have sufficient flaws that we're concerned that the association that's reported is not necessarily a true one.

So much of the judgment that went into putting studies in these various categories is not simply a matter of tallying up the pluses and the minuses or in some way averaging a whole group of studies which are taken with equal weight.

None of the studies are perfect. That's the nature of the beast and the nature of these kinds of investigations. They all have weaknesses, they have strengths. Part of the reason that this document is so thick is that there's an extensive discussion of the strengths and weaknesses and an explanation of how the committee came to its resolution. I wish we could boil it down to a justice system where we're weighing the evidence on one side and weighing the evidence on another side. It just simply doesn't—I think it doesn't come down to that simple a process.

Senator DASCHLE. I may have some additional questions along this line, but I note there's now a vote, and I actually just can't bring myself to holding you even longer here. I'm going to ask as many questions as my time will allow until I'm going to have to go vote, and then I'm going to adjourn the hearing and rely upon written questions for the balance so as not to take any more of your day.

You've recommended the development of new biomarkers for exposure and new exposure reconstruction models to facilitate further research. First, could you explain briefly, if it is possible, given the circumstances, why they're necessary, and, second, tell us if you're aware of any existing or promising work in the areas of biomarker or exposure model development?

Dr. FALLON. The only biomarker area that we investigated in any depth was that of dioxin measurement, which presumably contaminated approximately two-thirds of the Agent Orange lots and herbicides used in Vietnam. In that circumstance, the missing bit of information relates to the level 20 or 25 years after exposure in comparison to the individual's body fat, weight, serum lipids. There are a variety of confounding factors that make it very difficult for us to interpret all those years later exactly what a slightly or significantly elevated level means. It probably means exposure, but how much, when, and all those sort of things are difficult.

In the absence of an elevation—that is, a background that may be the same as your level or my level—that could possibly be compatible with having been exposed, but that the dioxin has been excreted in the intermediate time span. We don't know enough about human variability from one person to another in the rate of excretion of dioxin and the relationship to body fat, which is where it is stored, with the serum levels. That's the problem we have using that as a "gold standard" for even the two-thirds of the herbicides that contained dioxin.

Senator DASCHLE. So from what you've just said, I take it that it would be accurate to say that serum dioxin levels can verify that an individual was exposed to dioxin, but not that they were not exposed?

Dr. FALLON. Well, exposed, yes. Where and how much is uncertain. If it's background, as most Americans have—almost all of us have significant dioxin levels. If it's at that level, we can't prove that it might not have been higher at some other time. Now, they are useful, I think the committee agreed, in the aggregate. That is, if you take a group of 100 or 2,000 or 10,000 and we believe that they've been exposed in some way and the average of their dioxin levels are substantially increased, then that's meaningful.

Senator DASCHLE. What is the likely effect of general misclassification in an exposure index, as your report cites in the CDC Agent Orange study and the Ranch Hand study?

Dr. FALLON. Perhaps Jesse would reply to that one.

Dr. BERLIN. It depends on what type of misclassification you're talking about. I think the issue that we've been focusing on is what's known as random misclassification or nondifferential misclassification, which basically means if you're talking about classifying people as either exposed or unexposed, you're just as likely to make a mistake with somebody who goes on to get disease as with somebody who goes on not to get disease. So you're not generating an artificial association between disease and your error-prone exposure measurement.

Senator DASCHLE. I would think that you would underestimate a positive association——

Dr. BERLIN. That was my next sentence.

Senator DASCHLE. Oh, I'm sorry. I interrupted.

Dr. BERLIN. You will tend, in general, to underestimate those associations.

Senator DASCHLE. I realize that that wasn't your first point, but I think that it's the most important point, because studies like this for which there has been so much said and, frankly, so many conclusions drawn, unfortunately, tend to mislead people. In one Ranch Hand study, for example, you have misclassification and, therefore, an underestimation of positive association, and that then becomes the genesis of one of the problems we've had to deal with. Would you agree?

Dr. BERLIN. Yes.

Senator DASCHLE. Regarding veterans' exposure, would it be more accurate to say that we simply don't know enough about veterans' exposure and that we can't quantify the risk or that veterans weren't significantly exposed?

Dr. FALLON. Well, I think the last statement can only be made for some veterans, and we don't know what percentage of veterans were not significantly exposed. The major issue is, what subpopulations of veterans were exposed, and how heavily, and what does that mean in terms of health outcomes? One of the reasons for dwelling so long on the issue of industrial or agricultural or other kinds of exposures is that that is the comparison that we might be able to make, and those are the health outcomes, of course, we will be looking for in any new study of veterans that compares those who have significant exposure levels with certain health outcomes.

Senator DASCHLE. So what you're saying, Dr. Fallon, is that we really don't know whether veterans were significantly exposed, because we can't quantify the risk.

Dr. FALLON. Well, we can say that certain groups are. We do know about Ranch Hands and the Chemical Corps. The question is whether there are other subpopulations. The only study I'm aware of that measured serum dioxin—again, not a totally satisfactory measurement, but in a larger group of veterans—did not show elevation above background. So we know that some, as a group, don't seem to have major dioxin exposure. That doesn't exclude that they might have been exposed to something else, and it doesn't mean that there aren't other large subpopulations like Ranch Hands. That was the purpose of our new study, to search for those people.

Senator DASCHLE. Let me ask one last question. We've got five bells on, which means that we're down to a few minutes. To what extent could the committee distinguish, even on a limited basis, between the associations with TCDD exposure and associations with other herbicides? For example, is it possible to say that nonHodgkin's lymphoma is probably associated with 2,4–D and that soft-tissue sarcoma is probably associated with TCDD?

Dr. FALLON. The evidence and the literature would suggest that nonHodgkin's lymphoma is more likely to be associated with the herbicide 2,4–D than it is with dioxin. That's true. For the others, the association seems to be vest with dioxin itself.

Senator DASCHLE. Well, as I indicated, I have just innumerable more questions, and I intend to submit them, and I appreciate your indulgence. We may have more than one vote, which is why I'm not very confident about coming back any time in the near future. So let me submit them in writing and again reiterate my sincere gratitude on behalf of all Veterans' Committee Members and, I'm sure, Senators. You've done commendable work, and we are grateful to all of you.

With that, the hearing stands adjourned.

[Whereupon, at 1:05 p.m., the Committee was adjourned, to reconvene at the call of the Chair.]

APPENDIX

PREPARED STATEMENT OF CHAIRMAN JOHN D. ROCKEFELLER IV

Good morning, and welcome to this hearing. This is a red letter day in the effort to resolve the Agent Orange issue. We will focus on a report released this morning by the National Academy of Sciences. For the first time, an independent review of the scientific evidence shows there is a clear association between Agent Orange exposure and five diseases. It further shows there is a likely relationship between exposure and several additional diseases. Finally, the report indicates that for numerous other conditions, including reproductive and neurological effects, there is inadequate information to conclude a definite association—that is to say, there may be an association, but we just don't have the information. These are incredibly important findings.

Contrary to what the federal government has said for many years, the report also suggests that further epidemiological studies are possible and should be done, now. This is enormously encouraging.

NAS conducted an 18-month review under the Agent Orange Act of 1991, a law that originated in our Committee. The report is thorough, well-balanced, and scientifically impressive. It will be extremely useful to policymakers, including VA and Congress.

Agent Orange has been the subject of very emotional discussion and argument for over two decades. I am deeply committed to resolving the mystery about Agent Orange and ensuring that veterans who experience adverse health effects because of exposure are compensated. The NAS report advances us far in this endeavor. And equally important, it gives us hope that the mystery can indeed be resolved.

I plan to hold a followup hearing in September, after those interested in this issue have had a chance to review the NAS report.

I am enormously pleased to welcome our witnesses here today. We are extremely fortunate to have Dr. Harold Fallon, chairman of the NAS committee that conducted the review, and Dr. David Kriebel [KREE-bul], a member of that committee; Dr. Ken Shine, president of the Institute of Medicine at NAS; and my friend, and a friend and advocate for all veterans, the Secretary of Veterans Affairs, Jesse Brown.

Because the timing of this hearing coincided with the conferences for the budget reconciliation, we met with some difficulty in scheduling. I would like to thank Secretary Brown, especially, for his understanding and cooperation in the preparations that led up to the hearing.

It's with great pleasure and pride, that I announce that I will pass the gavel to my colleague, Tom Daschle, for the hearing. Since his days as a member of the House, Tom has been a strong, national leader on the issue of Agent Orange. He was one of the key authors of the law that made this report possible, the Agent Orange Act of 1991. Tom, I thank you for your tireless work in this area and for your tremendous contribution in getting us to this point. Our nation's veterans appreciate your leadership and I know they are better off today for having Tom Daschle in the United States Senate.

PREPARED STATEMENT OF SENATOR THOMAS DASCHLE

For many of us in this room—and for thousands unable to be here—it has been a long, difficult struggle. Vietnam veterans have been subjected to many indignities. Like those who fought before and after them, they faced the horrors of war. Unlike others, too often they faced an unappreciative public upon their return home. And, as we all know, they faced enemies they hoped were their friends—Agent Orange and other herbicides used as defoliants in the war. But many Vietnam veterans will tell you that their greatest indignity has been suffered at the hands of the govern-

ment that sprayed those herbicides and, for so many years, avoided responsibility for the consequences of that decision.

"To care for him who shall have borne the battle and for his widow and his orphan." Those words, spoken by Abraham Lincoln in 1865, appear at the entrance to the VA's Central Headquarters in Washington. Today should be remembered as the day we finally reversed the tide and started fulfilling that promise to Agent Orange victims and their families.

Today I am encouraged that the process is working. Never before have I felt able to say that with confidence. Although the process that we began through the Agent Orange Act of 1991 is just beginning, the quality and comprehensiveness of the report being released today by the National Academy of Sciences (NAS) suggest to me that, for the very first time, veterans and the American public have a solid reason to believe that their concerns about exposure to Agent Orange, dioxin, and other toxic chemicals are being taken seriously by people in a position to help address those concerns.

The report is the first of six reports on the possible health effects of exposure to Agent Orange and other herbicides used in Vietnam. It is essentially a baseline reading, with five follow-up reports to come over the next ten years as additional scientific evidence is developed. It answers some of our questions related to specific disease outcomes and recommends further research that may shed light on these issues. It should put to rest the chants of those who have claimed that "Agent Orange never hurt anybody," or that "We'll never be able to answer these questions."

The American people owe a great debt of gratitude to the sixteen scientists who, during the past eighteen months, without compensation immersed themselves in the scientific literature related to health effects of Agent Orange and navigated the political and emotional waters surrounding this debate. They must have known they risked taking a thankless job. But I want each of them to know that I and many others thank them. It is clear to me, from my review of the report, that they have done all that Congress asked with a high degree of professionalism and, perhaps even more importantly, that they understand the significance of this effort. I also want to thank the NAS staff for their support of this tremendous undertaking.

These scientific reports are valuable and important in their own right as state-of-the-art measures of the state of the science. I want there to be no misunderstanding about that. The Agent Orange Act of 1991, however, requires that the Secretary of Veterans Affairs use this report, and any other relevant scientific or medical information, to help determine which, if any, veterans' illnesses should be service connected for disability compensation purposes.

Secretary Brown has a history of concern about this issue, and he has assured us that he wants to do everything possible to ensure that Agent Orange victims are given the compensation they deserve as soon as the science can point us in the right direction. In addition to hearing from the National Academy of Sciences on where the science has taken us so far and what further study may be necessary, the Committee looks forward to hearing Secretary Brown's view of where we go from here in terms of policy.

PREPARED STATEMENT OF SENATOR DANIEL K. AKAKA

Thank you and good morning, Mr. Chairman. I'd like to join you in welcoming Secretary Brown, Dr. Fallon, Dr. Shine and other officials from VA and the National Academy of Sciences who are here to discuss the Academy's first report on the health effects of herbicides used in Vietnam, including Agent Orange.

The controversy over Agent Orange has been a painful one for Vietnam veterans as well as for those of us involved in developing veterans policy. The release of today's NAS report hopefully marks, if not an end, at least the beginning of an end to this national controversy.

Mr. Chairman, based on the report's findings, I believe VA should add Hodgkin's disease and PCT to the list of presumptively service-connected conditions, and to seriously consider adding respiratory cancers, prostate cancer, and multiple myeloma to the list. The NAS report's extensive recommendations for improving research on herbicide exposure should also be seriously considered.

Mr. Chairman, I should note that NAS' initial report is both good news and bad news. The bad news is that there is no longer any doubt that many serious diseases are in fact related to herbicide contact, and that as time goes by and latent diseases manifest themselves, we are probably going to see more diseases associated with exposure to defoliants used in Vietnam. The good news, if we can call it that, is that the report validates the presumptive policy toward the Agent Orange issue embodied in P.L. 102–4, the Agent Orange Act of 1991.

No one deserves greater credit for this policy than our Senate colleagues, Tom Daschle and John Kerry. Through sheer force of will, they impelled VA to make an about-face on this issue, and led the fight in Congress that, two years ago, resulted in the requirement for the NAS study itself as well as in the codification of non-Hodgkin's lymphoma, soft-tissue sarcoma, and chloracne as service-connected conditions. The report that is the subject of today's hearing is a tribute to their diligence, compassion, and foresight on this issue.

If there is an object lesson here, Mr. Chairman, it is that veterans should always be accorded the benefit of the doubt. If we had listened to their pleas for help from the beginning, we could have avoided years of anguish. But that is well in the past. We must now apply our experience with Agent Orange—both political and scientific—to the needs of other veterans who are in pain, such as Persian Gulf veterans who may have been exposed to environmental toxins during that conflict.

Thank you, Mr. Chairman. I commend you for holding this important hearing and look forward to reviewing the testimony of our witnesses.

PREPARED STATEMENT OF SENATOR BEN NIGHTHORSE CAMPBELL

Let me begin by commending the Chairman for convening this important hearing and congratulate the institute of Medicine's Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides for its hard work.

After twenty years of conflicting information and emotional debate, it is time that we settle this issue—the courageous veterans of the Vietnam War deserve nothing less. During the war, 19 million gallons of herbicides, like Agent Orange were sprayed over South Vietnam. As a result, about 35,000 veterans of that war have filed claims for coverage.

This report reinforces my belief that exposure to Agent Orange and other herbicides can be every bit as real and damaging as a bullet wound or a mine explosion.

I am pleased to see that the Secretary of the VA, in response to this report, has moved to add Hodgkins Disease, a form of cancer, and PCT, a blistering skin condition, to the list of service connected disabilities linked to herbicides. These two illness were found to be associated with exposure in the NAS report. This is certainly a step in the right direction.

I hope that as the Department considers the other aspects of this report it will move quickly on those health outcomes that have suggestive elements of an association, such as respiratory cancers, prostate cancer and multiple myeloma (mie-loma). I have great faith in our new Secretary of the VA, Jesse Brown, and like all other veterans across the nation, I look forward to his leadership.

Again, I look forward to today's testimony.

PREPARED STATEMENT OF DR. KENNETH I. SHINE, PRESIDENT, INSTITUTE OF MEDICINE

Mr. Chairman and members of the Committee, I am pleased to have the opportunity to testify before the Senate Committee on Veterans' Affairs on the Institute of Medicine's report prepared by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. I will provide a brief summary of the background on the committee's report and the Institute of Medicine. The chairman of the committee, Dr. Harold Fallon, will present a brief overview of the committee's findings and recommendations. Also seated with us is Dr. David Kriebel, a member of the committee, who is prepared to answer any questions.

In response to decades of concern surrounding the possible long-term health consequences of exposures to herbicides and the contaminant dioxin, Congress directed the Secretary of Veterans Affairs, in Public Law 102–4 signed on February 6, 1991, to request the National Academy of Sciences to conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used during the Vietnam conflict. The report from the Institute of Medicine's (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, "Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam" reviews and evaluates the available scientific evidence regarding the association between exposure to dioxin or other chemical compounds in herbicides used in Vietnam and a wide range of health effects, and provides the committee's best assessment of this body of knowledge for the Secretary of Veterans Affairs to consider as the Department of Veterans Affairs exercises its responsibilities to Vietnam veterans. The report also describes areas in which the available scientific data are insufficient to determine whether an associa-

tion exists and provides the committee's recommendations for areas in which future research is likely to be most productive.

The National Academy of Sciences was created by an act of Congress and signed into law in 1863 by President Abraham Lincoln, and is dedicated to the furtherance of science and technology and to their use for the promotion of general public welfare. The IOM was chartered by the National Academy of Sciences in 1970 to serve as an adviser to the federal government on issues that affect the public's health, as well as to act independently in identifying important issues of medical care, research, and education. The IOM brings to this mission more than two decades of experience in conducting independent analyses of pressing health problems that involve federal policy decisions.

The Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides' 16 members represent a wide range of expertise. The members voluntarily participated on the committee and served without compensation. The committee was chaired by Harold Fallon, M.D., Dean of the Medical School at the University of Alabama, Birmingham. David Tollerud, M.D., M.P.H., Director of Occupational and Environmental Medicine at the University of Pittsburgh, served as vice-chair. Committee member Norman Breslow, Professor of the Department of Biostatistics of the University of Washington, served as a liaison to the IOM Board on Health Promotion and Disease Prevention, which was responsible for overseeing this study.

All committee members were selected because they are leading authorities in their scientific fields, are well-respected by their colleagues and peers, have no conflicts of interest with regard to the matters under study, and, indeed, have taken no public positions concerning the potential health effects of herbicides in Vietnam veterans or related aspects of herbicide or dioxin exposure. The committee thus has provided a fresh analysis of this issue—which is both scientifically complex and emotionally charged—and this report reflects the committee's thorough and unbiased scientific judgments. As with all reports from the IOM, the committee's work was reviewed by an independent panel of distinguished experts.

PREPARED STATEMENT OF HAROLD FALLON, M.D., CHAIRMAN, INSTITUTE OF MEDICINE'S COMMITTEE TO REVIEW THE HEALTH EFFECTS IN VIETNAM VETERANS OF EXPOSURE TO HERBICIDES

Mr. Chairman and members of the Committee, I am pleased to have the opportunity to testify before the Senate Committee on Veterans' Affairs on the Institute of Medicine's report prepared by our Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. I will provide a brief overview of the committee's findings and recommendations.

A bitter legacy of the Vietnam War has been the decades of concern over the health effects of Agent Orange and other herbicides. More than 19 million gallons of herbicides were sprayed over South Vietnam in the years between 1962 and 1971, before reports of health effects in laboratory animals ended herbicide spraying. Most large-scale spraying took place from the air, but a considerable amount of spraying was also done from boats and ground vehicles and by soldiers carrying back-mounted equipment.

Since that time, some of the 3 million Americans who served in or near Vietnam have come to suspect that their wartime exposure to herbicides caused them to develop cancer or their children to have birth defects. This concern has helped initiate literally thousands of scientific studies on the health effects of herbicides and of dioxin, which contaminated about two-thirds of the herbicides used in Vietnam. Yet the issue remains shrouded in controversy and mistrust.

This issue has been a source of great anguish for veterans, for their families, and for the nation at large. Vietnam veterans made great personal sacrifices in serving their country. Yet they have faced continuing uncertainty about whether exposure to herbicides has led to past health problems or could lead to problems in the future. Some of these veterans and their families feel that their pain and suffering have been ignored and that these questions have not been adequately addressed.

Recognizing this uncertainty, the U.S. Congress passed the Agent Orange Act of 1991. That legislation asked the National Academy of Sciences to do a comprehensive review and evaluation of the available scientific and medical evidence regarding this issue.

The task was undertaken by a committee under the Institute of Medicine. Today, our committee is releasing its report.

To gather information for the report, the committee held three public meetings to allow veterans and other interested individuals to voice their concerns and opin-

ions. In addition, members of the committee and the staff sought and received information from a broad array of individuals and organizations, including veterans' groups, congressional committees, federal agencies, scientific experts, and the public. This wide-ranging dialogue contributed substantially to this report.

We studied both the toxicological and the epidemiologic data on herbicide exposures. After reviewing thousands of studies, we focused on approximately 230 epidemiologic investigations for detailed review and analysis. Most of these studies did not involve Vietnam veterans. Rather, they were studies of people who were exposed to herbicides as a result of their jobs or as a result of contact in the environment—for example, because of a nearby industrial accident. These types of exposures often were at high levels and for long periods of time. Getting a clear picture of the health risks for Vietnam veterans is not so straightforward because the levels of exposure were extremely wide ranging. Indeed, while most veterans probably had lower exposure levels, some may have experienced levels as high as that of occupational or agricultural exposures. What is uncertain is how many veterans may have been exposed to those higher levels and who those individuals are.

Based on the evaluations of the studies we reviewed, our committee found sufficient evidence of a statistical association between exposure to herbicides or dioxin and three types of cancer: soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. We also found sufficient evidence of an association with two skin conditions: chloracne and porphyria cutanea tarda, or PCT.

We found limited or suggestive evidence of an association between exposure to herbicides used in Vietnam and three other types of cancer: respiratory cancers, prostate cancer, and multiple myeloma.

For most of the other cancers, diseases, and disorders reviewed by the committee, the scientific data were not sufficient to determine whether an association exists. These include such cancers as bone cancer and leukemia and disorders ranging from birth defects to nervous system disorders.

However, for a small group of cancers, including gastrointestinal cancers and brain tumors, the committee found limited or suggestive evidence to conclude that there is *no* association between these cancers and herbicide exposure.

The greatest problem that we encountered in our study was a severe lack of information about the exposure of individual Vietnam veterans to herbicides. Except for particular groups, such as the individuals directly involved in spraying operations, information on the extent of herbicide exposure among veterans is practically nonexistent.

New biochemical techniques can detect low levels of dioxin in the blood, but we did not find that these measures are useful for arriving at *individual* exposures. People metabolize dioxin at different rates, and almost all Americans have some background exposure to dioxin. Furthermore, not all of the herbicides used in Vietnam contained dioxin.

This lack of data is why we were compelled to focus largely on epidemiologic studies of groups other than Vietnam veterans. We simply do not know enough about the exposures of veterans to determine to what degree they were or are at risk.

We do feel, however, that it is possible to develop better methods of determining exposures among individual veterans. Rather than relying on measures of dioxin in the blood, we recommend that exposure evaluations draw on historical reconstructions. These reconstructions take into account such factors as troop movements, ground and perimeter spraying, herbicide shipments to various military bases, the type of terrain and foliage typical of the locations sprayed, and the military missions of the troops located there.

Historical reconstructions require substantial professional judgment; therefore, the committee recommends that a nongovernmental organization be commissioned to develop and test models of herbicide exposure for use in studies of Vietnam veterans. These exposure models should in turn be evaluated by an independent scientific panel to determine their usefulness. The independence of these scientific groups would allay the public's concern about impartiality and scientific credibility.

If a better model of exposure can be developed, a number of important epidemiologic studies become possible. Highest priority should be given to those studies that could change the balance of evidence for or against an associated health effect. Research on reproductive effects should also receive priority.

In addition, our committee recommends that the study of the Ranch Hand cohort, which has been looking at the individuals involved in the Air Force's spraying program, be continued and expanded. A similar study should look at the members of the Army Chemical Corps and an appropriate comparison group. Both the Ranch Hand and the Chemical Corps veterans are known to have had significant exposure to herbicides.

Our committee was not asked to make judgments regarding individual injuries or the appropriate compensation for Vietnam veterans, and we did not do so. Rather, we were asked to provide information that the Secretary of Veterans Affairs could use in exercising the responsibilities of the Department of Veterans Affairs to Vietnam veterans.

Over the years, extreme views have evolved over this issue. On one extreme is the view that Agent Orange and dioxin cause a wide range of diseases; on the other is the suggestion that exposure to Agent Orange has not led to health problems. Our committee has determined through an extensive review of the scientific literature that, indeed, there does appear to be a link between exposure and certain diseases.

We believe that our report is a comprehensive, unbiased scientific review of the available evidence concerning this issue. This report will not end the controversy. But we hope that it will provide an agreed-upon base of information from which we can proceed to answer the questions that remain.

I would like to submit the Executive Summary of the committee's report for the record. That concludes my testimony. My colleagues and I are prepared to respond to any questions you and other members of the committee have.

PREPARED STATEMENT OF HON. JESSE BROWN, SECRETARY OF VETERANS AFFAIRS

Mr. Chairman, I would like to begin by expressing the appreciation of the veteran community, and my personal admiration, for the leadership that this Committee has shown in addressing this difficult issue.

Today's hearing marks a milestone in the search for the truth about Agent Orange. Since 1978 when the issue first surfaced, Vietnam veterans and their families have been waiting for definitive answers to their many questions about Agent Orange.

As a member of a veterans' service organization, I was aware of the fears and frustrations of my fellow Vietnam veterans. As Secretary of Veterans Affairs, I am committed to taking a fresh look at the issue and to doing the right thing. Vietnam veterans deserve no less.

As you know, one of the principal sources of frustration has been the inability of the scientific community to provide us with definitive answers about the health effects of exposure to Agent Orange. The conclusions reached in the scientific research that has been done were often conflicting and confusing. Every side of the controversy could point to some study to bolster their position on whether exposure to Agent Orange produced an adverse health impact. As the controversy dragged on, positions hardened and the dialogue became impassioned and emotional.

It was at least partially in response to this stalemate that the Congress mandated VA to contract with the National Academy of Sciences to perform an unbiased review of the scientific literature and offer its assessment. I must acknowledge the task was not an easy one for the Academy.

We are now assessing what they have said and will, within the time mandated by the Agent Orange Act of 1991, make the necessary decisions. There are some decisions, however, that need not await the full 60 day time period the Congress gave us in that law.

I am prepared to act right now on some of the Academy's recommendations; specifically, concerning those conditions for which they found scientific evidence sufficient to conclude that there is a positive association between exposure to a herbicide agent in Vietnam and subsequent adverse health.

I have directed the Veterans' Benefits Administration to begin the rule-making process to recognize Hodgkin's disease and porphyria cutanea tarda as being associated with exposure to herbicides used in Vietnam. No action need be taken with respect to soft-tissue sarcomas and chloracne, as VA has already recognized these as being associated with exposure. VA's rule regarding non-Hodgkin's lymphoma will be revised to reflect this disease's recognized association with herbicide exposure.

I have furthermore directed the Veterans' Benefits Administration to contact Vietnam veterans on the Agent Orange Registry who have the newly recognized diseases, and have not filed for compensation—to urge them to apply. I believe that this prompt action is appropriate, indeed, even mandatory.

I am not prepared today to render judgment about the Academy's report as it relates to other conditions. It is imperative, in my view, to fully analyze the implications of this report, and then to expeditiously act on the recommendations that arise from that review.

I therefore have established an internal, high-level panel to review the report and to solicit comments on it from other medical and scientific authorities, representa-

tives of veterans' service organizations and other interested parties. Dr. Susan H. Mather, VA's Assistant Chief Medical Director for Environmental Medicine and Public Health, will chair this panel. Membership will include top-ranking officials of the Veterans Health Administration, Veterans' Benefits Administration and General Counsel. The panel will advise me of their findings in time for me to make decisions within the 60 day time period.

I am also acting now to accept key recommendations of the Academy with respect to future research. I am keenly aware that Vietnam veterans have been waiting too long, and too often have been told to wait for more research. But I am persuaded by the Academy's reasoning that more research is needed if we are to ever be able to finally put this issue behind us.

I think the recommendations of the Academy are well presented and they appear to be soundly based. I have therefore asked the Under Secretary for Health to prepare an action plan that will implement the research recommendations in a timely manner.

I would like to comment specifically about several of the recommendations.

Perhaps the fourth recommendation is the most important: the Academy recommended exploring the feasibility of developing a method for historical herbicide exposure reconstruction for Vietnam veterans. I think this is a worthwhile proposal, and I have asked that steps be taken to accomplish this recommendation.

There are many conditions for which the Academy was unable to arrive at definitive recommendations. In large measure, this was due to inadequacies in the scientific literature, particularly with respect to verified exposure. If a method for determining exposure with greater certainty can be devised, we would be able to better focus our research and arrive at more supportable conclusions. Indeed, this may serve as a way to answer whether Vietnam veterans are at risk for adverse health due to Agent Orange exposure. Because it does have such potential importance, I have asked that this be given high priority for implementation.

The Academy also recommended that the Air Force Ranch Hand Study be continued with an external review by an independent, nongovernmental scientific panel. I have written to the Acting Secretary of the Air Force to urge serious consideration of this proposal.

The Academy additionally recommended that members of the Army Chemical Corps and an appropriate comparison group be followed in a study similar to the Ranch Hand Study. The recommendation said that this Chemical Corps study also should have oversight from an independent, nongovernmental scientific panel. VA is presently conducting a mortality and morbidity study of Chemical Corps personnel who served in Vietnam. Study results were reported on the mortality and morbidity experience of this group in 1990. No unusual findings were noted at that time.

VA researchers are currently working to expand this study to include Army Vietnam-era veterans with chemical occupational specialties who did not serve in Vietnam. The Department will seek to have this research project reviewed by an outside panel to determine if improvements can be made and we will submit the results to the panel for their review.

One Academy recommendation will require greater consideration: the suggestion that military personnel records be modified to include a marker for Vietnam service is a worthwhile one. VA will explore the feasibility of accomplishing this. It will require a coordinated effort among several departments and agencies.

I want to assure you and the Vietnam veteran community that I am approaching this issue with an entirely open mind. In those areas where I believe the Academy has made definitive findings, I have acted to implement them. As to the remaining areas, I will take the time provided by statute to satisfy myself that the action the Department takes is the right action, and that it puts veterans first and foremost.

I also want to note that I intend to pursue further discussion of this issue with the members of this Committee and of the House Committee on Veterans' Affairs. I am certain that working together we can achieve a just resolution.

WRITTEN QUESTIONS SUBMITTED BY CHAIRMAN ROCKEFELLER TO THE DEPARTMENT OF VETERANS AFFAIRS AND THE RESPONSES

Question 1. The Agent Orange Act of 1991 explicitly required VA's initial contract with NAS to provide for followup scientific reviews and reports at least every two years for ten years after the release of the first NAS report. What does the contract between the VA and NAS provide with respect to the followup reviews?

a. If there is no such provision in the contract, please provide the Committee with a General Counsel opinion supporting this interpretation of the Act.

b. Does VA intend to enter into another contract with NAS that would fulfill this agreement under the Act?

Answer. Public Law 102–4, the Agent Orange Act of 1991, required VA to enter into a contract with the National Academy of Sciences (NAS) for a scientific review of the possible adverse health effects of exposure to Agent Orange and other herbicides containing dioxin that were used in Vietnam. VA funded an initial 18-month review, results of which were recently announced by the NAS, using $956,000 in Medical and Prosthetic Research dollars. VA is proceeding, under terms of its current agreement with the National Academy of Sciences (NAS), to exercise its contractual option to provide for the continued review by the Academy through FY 1994. The Academy has requested an additional $156,000 to support this review and funds have been made available for that purpose. The agreement with the NAS will provide for the Academy's continuing review during FY 1994 and preparation of an interim progress report at year's end. VA will then exercise its option to extend the contract through FY 1995 following which the Academy will provide VA with a report of findings from its 2-year review. We intend, subject to the availability of funds, to negotiate an additional contract prior to the expiration of the existing contract to continue this effort as required by the statute. We intend to fully comply with the provisions of the law.

Question 2. The Agent Orange Act of 1991 requires the Secretary to initiate a blood and tissue archiving system to facilitate further research unless the Secretary, giving "great weight" to the NAS recommendations, determines that it would be of little scientific value of financially unfeasible. The Act gives the Secretary 90 days following the release of the NAS report to make a determination with respect to this provision, but at this point, what action does VA anticipate taking with respect to the blood and tissue testing and archiving programs addressed in the Act?

Answer. The NAS committee carefully evaluated the concept of establishing blood and tissue testing archiving programs. The NAS report concluded, "Balancing the strengths and weaknesses of stored biological samples and clinical data for research purposes, the committee feels that systems of this sort have scientific value, but only to the extent that they are components of specific, well-designed studies; see, for instance, National Research Council (1991). In the absence of a clear study design to guide such activities, and without resolution of important design, quality control, and ethical issues regarding tissue banks, the committee does not recommend the establishment at this time of the clinical data and tissue archiving systems described in sections 6 and 7 of the law." While no final decision has been made by the Secretary regarding this matter, we do not anticipate implementation of this program in the immediate future. If a clear study design can be prepared and other obstacles cited in the report overcome, additional consideration will be given to this idea.

Question 3. Please clarify VA's intent with respect to the NAS recommendation for all military service records to be "flagged" for Vietnam service. Can this be done? How long would such a project take? How much would it cost?

Answer. VA is giving serious consideration to the recommendation. No final decision has been made regarding this matter. The identification of all Vietnam theater veterans is possible through review of their personnel records archived at the national Personnel Record Center in St. Louis. However, doing so is very labor intensive because a review of all 9 million records of Vietnam era veterans would be required to identify the approximately 2.5 million Vietnam veterans.

Assuming at least 10 minutes record handling time for each record, it will take 1.5 million man-hours to complete the record review. That is about 750 person years. The cost of the project based on manual record review may amount to tens of millions of dollars.

Alternatively, we are exploring the feasibility of accomplishing this recommendation, at least in part, by using computerized/automated data bases maintained by the Defense Manpower Data Center (DMDC) within the Department of Defense and by VA.

In addition, we will attempt to obtain the names of Vietnam veterans who received bonuses offered by individual states for their service in Vietnam. We know that at least 20 states provided bonuses to Vietnam veterans. Vietnam service indicators in the DMDC computer files and state bonus recipients rosters need to be evaluated for accuracy.

The extent of the manual record work required to complete "flagging" of all veterans who served in Vietnam is unknown at this time. We will have more concrete estimate of the time and the costs involved in a month.

Question 4. Are Persian Gulf records currently being "flagged," or is an effort being made to begin doing so?

Answer. Both VA and DoD have an automated roster of all military personnel who served in the Persian Gulf Theater of Operations. This file gives VA the capability to analyze VA health care data for all Persian Gulf Veterans. All Persian Gulf medical records currently are being "flagged." These include the following Persian Gulf Veterans, who:

- voluntarily participate in the Persian Gulf War Veteran Registry Examination Program;
- receive outpatient care associated with service in the Persian Gulf;
- have filed claims for compensation on the basis of any disability that may be associated with such service;
- have died and are survived by spouse, child or parent who filed a claim for dependency and indemnity compensation on the basis of such Persian Gulf service.

Question 5. What can Congress do, if anything, to facilitate any of the NAS recommendations regarding further research?

Answer. We do not anticipate that congressional action will be necessary to act upon the NAS recommendations regarding future research. Of course, we will look to Congress to provide adequate funding for any large-scale research projects.

WRITTEN QUESTIONS FROM CHAIRMAN ROCKEFELLER TO THE NAS COMMITTEE TO REVIEW THE HEALTH EFFECTS IN VIETNAM VETERANS OF HERBICIDES AND THE RESPONSES

Question 1. The Agent Orange Act of 1991 explicitly required VA's initial contract with NAS to provide for followup scientific reviews and reports at least every two years for ten years after the release of the first NAS report. Will NAS be conducting some or all of the five followup reviews mandated in the Act? If the contract did not provide for followup review and reports, are there any advantages to having NAS, rather than some other nongovernmental scientific organization, conduct subsequent reviews because of NAS' experience conducting the initial review? What can Congress do, if anything, to facilitate this process?

Answer. Section 3(g) of the Agent Orange Act of 1991 specifies that the NAS, or other independent, scientific organization shall submit reports at least once every two years, from the date of the first report; these follow-up reviews are subject to Congressional authorization and appropriation. The contract with the Department of Veterans Affairs for the initial NAS review expired July 31, 1993. The DVA has subsequently contracted with the NAS for additional dissemination activities and to conduct a committee meeting over the next two months. In addition to Congressional appropriations, subsequent reviews by the NAS will require approval by the Governing Board of the National Research Council, which we will, but have not yet sought.

Question 2. In the report, the committee suggests that the scientific evidence in this area is growing—that many of the important studies were published just recently. Is the scientific knowledge in this area expanding at a rate that would support the statutory requirement for followup reviews and reports every two years?

Answer. The committee believes that the scientific literature in this area is growing and will continue to expand. Several studies that the committee valued as particularly important to their evaluation were published during the last two years. Since the release of their report, the committee has learned of other relevant papers that will be published later this year.

Question 3. In general terms, did the committee observe any scientific trends reflected in the most recent evidence? (Are the recent studies mostly suggestive of an association, or mixed? Are there different trends in different areas? Is the evidence pointing in certain directions?)

Answer. There are no apparent observed trends in the more recently published studies. In evaluating these studies, it is important to be aware of latency issues—that is, the period of time that has elapsed since exposure and the observance of health effects, particularly studies of herbicide exposure and some types of cancers. For many studies, the committee noted that insufficient time had passed since exposure for many types of tumors to develop. Further study of these outcomes are warranted.

Question 4. The disease outcomes within categories are not listed in alphabetical order. Is there any significance in the order in which they are listed?

Answer. In Chapter 8 on cancer, the various cancer types are discussed according to their International Classification of Disease (ICD) order. In the chapter on reproductive effects, the disorders are described in accordance with the stages of the reproductive cycle, i.e., beginning with the review of spontaneous abortion, followed

by birth defects perinatal and infant mortality, childhood cancers, and finally infertility. In the remaining health outcome chapters, specific health effects are described in a logical order defined by broad health categories.

Question 5. Is the level of confidence of the positive associations for non-Hodgkin's lymphoma, soft-tissue sarcoma, or chloracne any different from that for the positive associations for Hodgkin's disease or PCT?

Answer. The committee was unable to make distinctions within each of the four categories as to the strength of the evidence for an observed association.

Question 6. The committee focused on 230 studies chosen from thousands of documents. What procedure did the committee follow for choosing the 230 studies? What standard did the committee use to choose them? Were the studies chosen of higher quality, or was there some other consideration (for example, did the committee include some studies because they were well-known, controversial, etc.)?

Answer. The committee's focus on the 230 studies was based on the fact that these studies included the minimal standards for epidemiologic research, that is, they included some measure of relevant herbicide or TCDD exposure and information on health outcome. Excluded from this group were toxicologic studies in animals and secondary literature, such as review articles and discussion papers. The committee did not rank studies for consideration based on their quality or whether they were "well-known or controversial." However, the most scientifically well designed studies and those with the largest groups under study were given more weight in developing our conclusions.

Question 7. Could someone reading the report determine which studies the committee found to be of high quality and which the committee found to be of more questionable quality?

Answer. As noted above, the committee did not rank individual studies based on their quality, however, the quality of the statistical and analytical methods employed did bear on the committee's assessment of whether the evidence was supportive or suggestive of an association, suggestive of *no* association, or was inadequate for determining whether an association did exist. The methodology for each of the 230 studies reviewed is described in Chapter 7; critiques of these studies are included under the appropriate health outcome discussion.

Question 8. When the committee reviewed each of the 230 studies—the Ranch Hand Study, for example—what level of review was undertaken? Did the committee ever review the original data, or was the review limited to the findings as reported by the study authors?

Answer. The committee reviewed and evaluated published epidemiologic and toxicologic studies. In all cases, these studies were reviewed by at least one, and most of the time by two or more committee members plus staff. The committee did not conduct any original data analyses.

Question 9. With respect to several government studies—the Ranch Hand Study is one—concerns have been expressed in the past that the findings, as reported in study reports, executive summaries, or the press, have not always reflected the data or the original manuscripts. Did the committee's review detect any such discrepancies in any of the studies? If so, how were the discrepancies resolved?

Answer. The committee makes specific recommendations regarding reanalyses of the Ranch Hand data, and particularly had concerns about the presentation and statistical analysis of the reproductive outcomes. The committee's concerns are explicitly stated in Appendix C. The committee was also aware that the Centers for Disease Control's Agent Orange Study was canceled; however, it was not in the committee's charge to judge the rationale for this decision. In the course of its work, the committee heard other allegations of scientific misconduct and claims of a government conspiracy to suppress information on health effects, as well as serious disagreements among scientists about the interpretation of laboratory and clinical data. The committee was not charged with investigating or resolving these controversies, and it did not attempt to do so. The committee took these issues into consideration only to the extent that they had a direct bearing on the scientific results that are the subject of this review. Because none of the committee's conclusions were based on single studies, we are confident that our conclusions are not dependent on fraudulent data.

Question 10. The committee recommends the development of a new exposure reconstruction model—or models—to facilitate further research. First, please explain why such a new model is necessary; and, second, indicate whether the committee is aware of any existing or promising work in this area (research involving veterans or others).

Answer. The exposure reconstruction model was recommended to estimate the likelihood of individual veteran exposure to herbicides in Vietnam. Such estimates for Vietnam veterans rarely exist in the epidemiologic literature. The committee in-

dicates several types of information that might be included in these models, i.e., information on troop location and aerial herbicide spray data, military indications for herbicide use, environmental persistence of the herbicides and TCDD, less formal sources of data on the use of herbicides and information from structured interviews. This type of historic exposure reconstruction modeling has been practiced quite successfully in some occupational epidemiology studies, and in recent years, considerable research has been done to develop systematic methods of historic reconstruction of exposure. An excellent example of this approach is provided by a large multicenter case-control study of hematolymphpoietic cancers being conducted in Italy and focusing on pesticides and solvents risk factors. In the participating centers, which are located in different agricultural regions, detailed job exposure matrices (JEMs) have been developed by agronomists with experience in local pest control practices. These JEMs estimate for each job, the types of chemicals likely to have been used, and if possible, their likely intensity of use. Subjects in the study who report employment in farming are asked detailed questions regarding the crops they grew and the pests they treated in the course of their working lives. Local agronomists who advise farmers on pesticide usage then can predict with some reliability which chemicals were used in that particular zone in a particular time period to combat the reported pest. If validated, this approach may be useful in addressing the questions remaining with regard to Vietnam veterans.

Question 11. The report cites the work in Vietnam of Dr. Schecter of State University of New York and Dr. Constable of Harvard, as well as the work of Vietnamese researchers on the health effects of exposure to herbicides. Would the committee recommend the continuation of feasibility studies by American researchers relating to exposure assessment and health effects in Vietnam?

Answer. Studies of the Vietnamese population exposed to herbicides are also possible and potentially useful. These studies might include Vietnamese still in Vietnam or perhaps even those now in the United States. Accurate disease ascertainment and exposure reconstruction may pose difficult problems, however. The actual exposure of this group to herbicides would be extremely difficult to determine accurately because (1) serious problems with recall bias are likely; (2) given war conditions, documents about location during the Vietnam conflict are unlikely to be completely available or reliable; and (3) the Vietnamese in question may have relocated in the intervening decades. Current serum TCDD measures may not be practical or relevant for the same reasons discussed above for U.S. veterans. Before significant resources are committed to studies of the Vietnamese population, the committee recommends that feasibility studies of both exposure reconstruction and disease outcome monitoring be conducted.

Question 12. With respect to confounding factors, can they be misleading in either direction, i.e.. can they result in either an underestimation or overestimation of risk?

Answer. Confounding occurs when the exposed and nonexposed groups are not comparable in terms of risk factors (other than the one under study) for the disease in question. To be a confounding risk factor, a variable must be associated with both the exposure and the disease under study. Depending on how the confounder is operating, the risk may be over- or under-estimated.

Question 13. Please explain the "healthy worker" or "healthy veteran" effect and any implications it may have on the interpretation of the various study results or on the extrapolation of occupational studies to veterans.

Answer. A source of bias that is often a problem in occupational studies with external comparison groups has been termed the "healthy worker effect." The general population which often comprise the comparison group, contains people who are too ill to be members of the work force. Since exposed workers, by definition, have to have been healthy enough to be in the work force, they as a group may be healthier than the general population of the same age and sex. Comparisons between these groups would tend to result in associations between exposure and disease which are biased toward the null, or in the direction of no association. The result of the healthy worker effect is to yield an underestimate of the true magnitude of association between exposure and disease. It is likely that the healthy worker effect applies to studies in which veterans are compared to nonveterans as well, and this possibility needs to be considered in interpreting some studies. The healthy worker effect, like other biases, cannot be removed in the analysis of data but may be avoided with an appropriate study design. The comparison group should be selected to be similar to the study group in socioeconomic and employment status in order to avoid the healthy worker effect. In particular, since a strict medical examination is part of military induction processes, in order to avoid or reduce the healthy worker effect it is preferable to compare Vietnam veterans to other Vietnam-era veterans than to those who did not serve in the military.

Question 14. The report mentions the difficulty in defining the class of soft-tissue sarcomas, but notes that they share a common International Classification of Diseases code. How should the class be defined, if it were to be as inclusive as possible?

Answer. Soft-tissue sarcomas (STSs) appear in as many as 28 histological types with 14 subtypes, and the causes of these diverse disorders may differ. These tumors may arise anywhere in the body and include fibrosarcoma and malignant fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, liposarcoma, synovial cell sarcoma, and angiosarcoma. Accurate diagnoses of STS can be difficult; because of the diversity and rarity of STSs, the average pathologist may not have detailed knowledge of the differential criteria, and even specialists in STS pathology disagree on some types. Overall, there is no clear histogenetic basis for registry classification of soft tissue sarcomas. However, the ICD codes (International Classification of Diseases—9 codes 171.0–171.9) considered in the committee's report represents the very inclusive class.

Question 15. Is there any scientific reason to exclude specific sarcomas from the findings of sufficient evidence of an association—specifically, osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma?

Answer. The epidemiologic studies on soft-tissue sarcomas that the committee reviewed generally grouped all types of soft-tissue sarcomas (ICD codes 171.0–171.9); results were not given for individual subtypes because the few cases per type would probably be insufficient for reliable statistical analysis.

Question 16. Are there any actions veterans—especially those who believe they may have been heavily exposed to herbicides—should take to ensure they receive proper medical follow-up? Does the committee have any recommendations for physicians who may be treating such veterans?

Answer. The committee did not address either of these issues and cannot comment.

Question 17. While acknowledging the usefulness of a blood and tissue archiving system to facilitate further research, the committee recommends postponing action on this until a valid exposure reconstruction model is developed and further studies utilizing that model are planned. Since serum dioxin levels decrease over time, and since it has been many years since veterans were potentially exposed to dioxin in Vietnam, what might be the consequences of delaying the acquisition of blood and tissue samples? Would consideration of those consequences cause the committee to modify its recommendation in any way?

Answer. The committee made its recommendation on the basis of all of the available information as of the time of its report. In particular, the committee is aware that serum TCDD levels decline over time, but in light of the negative features of blood and tissue archiving systems that are not components of specific, well-designed scientific studies, the committee did not recommend the establishment of such systems. Because all recommendations must be reviewed by the full committee and the National Academy of Sciences' report review process, we are not able to reconsider any recommendations at this time.

STAFF FORUM ON FUTURE RESEARCH ON AGENT ORANGE

TUESDAY, NOVEMBER 2, 1993

The Committee staff met, pursuant to notice, at 10 a.m., in room SR–418, Russell Senate Office Building.

Present: Senator Daschle.

Mr. GOTTLIEB. Good morning. We are waiting for the arrival of Senator Daschle, who is going to open our staff forum, as we are now calling it. I am Jim Gottlieb with the Committee. I want to explain what has probably been explained to most of you informally.

Because of the situation on the Senate floor, no committee can meet this morning officially. Matters are being taken up on the floor which the Majority Leader has determined should not be interrupted, and who are we to second-guess that as staffers?

We do very much want the input of the people who are at the table. We have asked the staffs of all of the Members who want to participate, as well, to come to the table. We had planned to conduct this hearing as a roundtable discussion in any event because we think for this situation that would be the best way to get the input of the people at the table. So we intend to proceed in that manner, take the presentations of the five "witnesses," and then proceed.

So, with that introduction, here is Senator Daschle. [Laughter.]

OPENING STATEMENT OF SENATOR THOMAS A. DASCHLE

Senator DASCHLE. Well, Madam Chairman—[Laughter.]

Ms. PETROU. Very funny.

Senator DASCHLE. Let me just apologize profusely for yet another mixup in schedule. We just never know what the Senate may bring, and it has brought us a nightmare on the Senate floor with Senator Packwood and the subpoena business. But I must tell you that we at the Committee on Veterans' Affairs felt that the urgency of this scientific issue demanded that we address it, that we wanted an opportunity to pick what we thought were the best minds on the issue nationally to build a record, and to seek your advice on many of the outstanding issues related to the National Academy of Sciences' work and our response to it. So that is the purpose of the hearing.

As I understand it, there will be an official record of it, Jim?

Mr. GOTTLIEB. Yes. An official record of an unofficial meeting.

Senator DASCHLE. Exactly. We will use the information presented today, and we will continue to build the hearing record and perhaps pursue additional meetings of this kind at a later date.

We also have a vote on the floor right now, so I will have to excuse myself. But I want to thank you all genuinely for coming, for again reorganizing your schedule to allow for this meeting. We hope very much it will be a productive session. Thank you.

Mr. GOTTLIEB. As was the case in our official hearing in July, it was Senator Rockefeller's intention to hand the gavel and the Chair for this hearing over to Senator Daschle. In following with that commitment, Laura Petrou, Senator Daschle's legislative director, will chair this forum.

Ms. PETROU. Thanks. What I thought I would do is to read the statement that Senator Daschle might have made had he been able to stay, to define the purpose is of this meeting. I will also go ahead and introduce the witnesses, and then we will hear from the witnesses for about 5 minutes each. Then maybe I will lead off with just a few questions, and then we will open it up to the other staff members who may have questions. So, the following is Senator Daschle's statement.

On July 27, at a hearing before this Committee, the National Academy of Sciences released its first report pursuant to the Agent Orange Act of 1991, reviewing the scientific evidence related to the possible health effects of exposure to Agent Orange and other herbicides used in Vietnam. While much attention was given to the report's discussion of disease outcomes, and rightfully so, one of the most important aspects of that report received little public attention at the time it was released.

The research recommendations in the NAS report provide an important framework for today's discussion of where the search for the truth regarding Agent Orange has taken us and where we need to go from here. Just as important will be the discussion of how we get there. The scientists who have quietly done some of the most promising work in this field, sometimes in the face of overwhelming odds, are here today to answer those questions.

Specifically, Congress and the scientific community need to focus on what research efforts offer the most realistic promise for finding reliable answers at a reasonable cost, how to develop accurate measures of exposure, and how to ensure that these scientific efforts are conducted and reviewed with absolute integrity. Once we define our research goals and methods, we will need to determine how the Government should facilitate their implementation.

There is a long history of Government involvement in this issue, but it is not a very proud history. This Committee takes very seriously its responsibility to ensure that the Government learns from its past mistakes and fulfills its commitment to the Vietnam veterans and their families who have suffered as a result of their exposure to Agent Orange. I am confident that today's discussion will lead us in that direction.

[The prepared statement of Senator Daschle appears on p. 84.]

Ms. PETROU. We want to welcome the witnesses here today and introduce them.

Richard Albanese is chief of the Mathematical Products Division at the Armstrong Laboratory at Brooks Air Force Base in San Antonio, Texas. Dr. Albanese is a physician and statistician with a background in both Government research related to Agent Orange and his own research in this and related areas. He is a former

principal investigator on the Air Force's Ranch Hand Study and has done extensive work in radiation analysis. He is an advocate of balanced peer review structures and other built-in measures to ensure the integrity of scientific pursuits.

Peter Kahn is associate professor of biochemistry in the Department of Biochemistry and Microbiology at Rutgers University. Dr. Kahn has a Ph.D. in Biochemistry and is the former principal investigator on the New Jersey Agent Orange Commission's Point Man Project designed to assess dioxin exposure in Vietnam veterans. He has served as a technical consultant to State and local governments struggling to address complex environmental cleanup issues.

Arnold Schecter is not here, I see. Dr. Schecter is probably the leading scientist doing work in Vietnam. We have his testimony, which we'll incorporate into the record as well.

[The prepared statement of Dr. Schecter appears on p. 123.]

Ms. PETROU. Ellen Silbergeld is senior toxicologist for the Environmental Defense Fund and professor of epidemiology and toxicology at the University of Maryland School of Medicine. Dr. Silbergeld has a Ph.D. in toxicology and was recently chosen as a MacArthur Fellow. Did I get that wrong?

Dr. SILBERGELD. I actually have a degree in engineering.

Ms. PETROU. OK. Dr. Silbergeld serves on the Ranch Hand Advisory Committee and has been involved in EPA's ongoing reassessment of the risk of exposure to dioxin.

Jeanne Stellman is associate professor of public health at Columbia University. Dr. Stellman has a Ph.D. in epidemiology. Is that correct?

Dr. STELLMAN. Physical chemistry.

Ms. PETROU. I'm wrong again. OK. Along with her husband, Steven, who is also here today and I'm sure could answer questions if we have them for him, Dr. Stellman has authored the epidemiological study known as the "Columbia University Studies of Vietnam Veterans and Their Exposure to Agent Orange."

David Tollerud is the vice chairman of the National Academy of Sciences Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. Dr. Tollerud is also the director of occupational and environmental medicine at the University of Pittsburgh.

I know that Dr. Mike Stoto is here too, if he needs to answer any questions from the NAS perspective.

So, with that, I guess——

Mr. GOTTLIEB. Before we proceed, perhaps we could go around the table and introduce ourselves.

Mr. WEAVER. Eugene Weaver. I am here representing Senator Specter.

Ms. EDDY. I'm Tammy Eddy and I am here representing Senator James Jeffords.

Mr. BEST. I'm David Best with Senator Thurmond's office.

Mr. BALLAND. Dave Balland, representing Senator Al Simpson's office.

Mr. TUERK. I'm Bill Tuerk. I am with the minority staff of the Committee and I am representing the Ranking Member, Senator Frank Murkowski.

Mr. BREW. I'm Bill Brew with the majority staff of the Committee.

Ms. MORROW. Meg Morrow, also with the majority staff of the Committee.

Mr. KIFER. Gerry Kifer of Senator Daniel Akaka's staff.

Ms. WASULA. Chris Wasula with Senator Graham.

Ms. PETROU. OK. Maybe what we can do is start with Dr. Tollerud, who can remind us all of what the research recommendations in the NAS report were. That can be a starting point for us.

STATEMENT OF DAVID TOLLERUD, M.D., VICE CHAIRMAN, COMMITTEE TO REVIEW THE HEALTH EFFECTS IN VIETNAM VETERANS OF EXPOSURE TO HERBICIDES, NATIONAL ACADEMY OF SCIENCES, AND DIRECTOR OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE, UNIVERSITY OF PITTSBURGH

Dr. TOLLERUD. Good morning. I am David Tollerud, director of Occupational and Environmental Medicine at the University of Pittsburgh Graduate School of Public Health, and vice chairman of the Institute of Medicine's (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. I am pleased to be here on behalf of the IOM Committee to address issues related to research on the health effects of Agent Orange and other herbicides used in Vietnam, and in particular, to clarify issues raised in the IOM Committee's report.

I will abbreviate my oral presentation, but I would like to have the entire written testimony entered into the record.

As you will recall, at your Committee's hearing on July 27, 1993, Dr. Kenneth Shine, president of the IOM, and Dr. Harold Fallon, chairman of the IOM Committee, provided your Committee with a brief summary of the background on the committee's report and the Institute of Medicine as well as the committee's recommendations about exposure reconstruction modeling and other research matters. I won't repeat that information again. I am prepared, however, to answer any questions about these recommendations that the Committee may have. For the record, we have included a full copy of Chapter 12 of the IOM Committee's report as attachment 1 to this statement. This chapter lays out and justifies the IOM Committee's research recommendations. We are also including a copy of appendix C: Methodological Observations on the Ranch Hand Study as attachment 2.

Today, in my oral testimony, I would like to address three specific issues: First, the role of serum dioxin measurements in future research efforts; second, the Ranch Hand Study; and third, the role of scientific advisory committees in further research on the effects of herbicides in Vietnam veterans.

First, regarding the role of serum dioxin measurements in future research efforts. Since our report was released, we have become aware that some scientists have misinterpreted our conclusions as saying that serum dioxin measurements have no value in epidemiologic studies. Our report does not say this, and we would like to set the record straight that this is not the IOM Committee's belief. The IOM Committee does, however, feel that serum dioxin measurements are not a "gold standard" of exposure to herbicides in Vietnam, and they should not be relied upon as the sole measure

of individual herbicide exposure in epidemiologic studies of Vietnam veterans.

To explain this conclusion, I will address each of the scientific points underlying it. First, the IOM Committee found that all Americans have some exposure to TCDD, or dioxin. Thus, even a veteran with an elevated dioxin level cannot be assumed to have been exposed to herbicides in Vietnam.

Second, not all herbicides used in Vietnam contained dioxin. This means that a veteran with a normal dioxin level may still have been exposed to herbicides in Vietnam.

Third, there are relatively large laboratory measurement errors associated with serum dioxin measurements. This does not imply poor laboratory practices; indeed, the CDC dioxin laboratory is an excellent laboratory and their measurements are remarkably precise for this kind of work. It does mean, however, that quantitative serum dioxin measurements for individuals are inherently imprecise, and that this variability needs to be explicitly taken into account in epidemiologic studies.

Fourth, and perhaps most importantly, there remain poorly understood variations among individuals in TCDD metabolism. These findings suggest that while serum dioxin measurements are not a gold standard, they can contribute to epidemiologic studies if properly included in the statistical analysis. Serum dioxin measurements can also contribute to the evaluation of the proposed historical reconstruction model. The Institute of Medicine believes, however, that serum dioxin measures need not and should not be the sole source of information on exposure to herbicides in epidemiologic studies of Vietnam veterans, and studies should not be designed solely around serum measurements.

Now, with regard to the Ranch Hand Study. As the IOM Committee noted in appendix C, because the veterans of Operation Ranch Hand are among those with the highest exposure to herbicides in Vietnam, because that exposure is well documented by records and serum dioxin measurements, and because this group has been the focus of extensive epidemiological and clinical observation, the Ranch Hand Study represents one of the best available opportunities for understanding the health effects of exposure to herbicides in Vietnam veterans. The IOM Committee thus reviewed all of the research reports concerning the Air Force's Ranch Hand Study in great detail.

The IOM Committee concluded, and I quote, "Much can be learned by reanalysis of existing data or more indepth analysis of data expected from current research programs investigating the health of Vietnam veterans, including the Air Force Ranch Hand Study and DVA studies of other highly exposed Vietnam veterans such as members of the Chemical Corps."

The IOM Committee has also recommended that priority be given to additional research on reproductive outcomes that would help clarify the possible effects of herbicides.

In the course of its review, however, the IOM Committee identified a number of methodological problems with the analysis and presentation of the data collected in the Ranch Hand Reproductive Effects study. The committee is aware of logistical difficulties involved in such a large and detailed data collection effort, and it ap-

plauds the efforts of the Air Force research team in that regard. In addition, the committee also acknowledges the efforts of the Ranch Hands themselves to participate in the followup study; they deserve a great deal of appreciation for their efforts.

The Air Force has prepared a background paper dated September 13, 1993, in response to the IOM Committee's appendix and other discussion of the Ranch Hand Study. Members of the IOM Committee and I were grateful to receive this background paper, and we have read and considered it carefully and will certainly take it into account in any future reviews of the Ranch Hand results. The Air Force background paper fairly characterizes our comments in two categories.

First, we noted that many aspects of the Ranch Hand report were difficult to understand. With regard to these issues, the IOM Committee was pleased to learn that some of the analyses and tables that it could not find are indeed in the report. We appreciate this explanation. However, after reviewing these tables, the committee does not feel that inclusion of the tables alters the committee's criticism of the report.

Second, most of our comments in appendix C relate to differences of scientific judgment regarding statistical methodology. The IOM Committee recognizes that there are often legitimate differences among scientists about how best to analyze data, and we are pleased that a public discussion about the best ways to analyze the existing data has begun. However, having considered the specific rationale offered by the Air Force in its "background paper" for the choices its analysts made, the IOM Committee stands by its original critique and recommendations.

The IOM Committee recognizes the possibility that extensive reanalysis of the data may not uncover any consistent positive findings. However, given the lingering questions in the minds of many about the association between reproductive effects and herbicide exposure, we feel that priority should be given to a reanalysis of the important Ranch Hand data by other scientists.

And finally, the role of scientific advisory committees. The IOM Committee made recommendations regarding an independent, nongovernmental scientific advisory panel for the proposed Ranch Hand and Army Chemical Corps studies. The IOM Committee made a separate recommendation that a nongovernmental organization be commissioned to develop and test models of herbicide exposure for use in studies of Vietnam veterans and a second scientific advisory panel to evaluate the proposed historical exposure reconstruction models. Although these three groups would serve different purposes, the IOM Committee believes that independence from Government is paramount to assure the scientific credibility of these groups.

The conclusion of a committee of the National Academy of Sciences convened to review the proposed protocol for the Ranch Hand Study, published by the NRC (National Research Council) in 1980, is as relevant today as it was more than a decade ago. Public perception of the Federal Government's interest in the outcome of the scientific studies related to herbicide exposure suggests that all such studies be conducted by nongovernmental organizations. Independence from governmental influence is needed in order to satisfy

the public's concern about impartiality and scientific credibility. The membership of these scientific advisory committees is also critical. They must have the appropriate disciplinary expertise as well as independence of mind. Both of the advisory committees that we recommend require expertise in biostatistics and epidemiology as well as exposure assessment. The advisory committee called for in Recommendation 6 will need special expertise in historical exposure reconstruction in occupational settings.

The IOM Committee carefully considered the issue of future research in this area. We hope that these recommendations will prove useful to those who must plan and implement a strategy to address the important questions which remain.

That concludes my prepared remarks. Thank you.

[The prepared statement of Dr. Tollerud appears on p. 85.]

Ms. PETROU. Dr. Albanese. We will go in alphabetical order; how's that?

STATEMENT OF RICHARD A. ALBANESE, M.D., CHIEF, MATHEMATICAL PRODUCTS DIVISION, ARMSTRONG LABORATORY, BROOKS AIR FORCE BASE

Dr. ALBANESE. Thank you. In my oral testimony, I will address the conduct of Government dioxin studies. The opinions expressed are my own and are not necessarily those of my employer, the U.S. Air Force.

Occupational, environmental, and public health questions are often associated with conflicting public and private interests and values. Therefore, in my view, it is very important that procedures and customs be put in place so that medical scientists studying these questions are well protected from the appearance and possibility of genuine conflict of interest. With respect to dioxin studies in veterans and other similar studies, I recommend three actions: (1) routine use of quality, balanced, fair peer review; (2) easy availability of data used to compose Government reports; and (3) the development of programs supporting academic freedom in occupational, environmental, and public health research facilities.

With respect to peer review. Published reports with an important bearing on veteran or general public health should have carefully balanced peer review. The peer review group should be balanced by containing contingents from all interested parties. In the case of dioxin, there should be governmental representatives, academic representatives, industrial representatives, participants who actively and emphatically communicate with veterans' groups, and representatives of the general public who can consider economic and health concerns. Leadership of the peer review group should be held by the most disinterested party or individual.

The peer review group should examine scientific methods and evaluate results for scientific rigor. Evaluation of complex health data has a subjective dimension. Therefore, the peer review group should ensure that the complete spectrum of scientifically tenable opinions is represented fairly. Active participation of many viewpoints reduces bias. I recommend that academic, industrial, Government, veteran, and general public groups remain actively engaged in the dioxin herbicide issue.

If a peer review group gets too large, it becomes logistically unmanageable and inefficient. Thus, it is unavoidable that important scientific disciplines and capabilities are not represented even on a well balanced peer review group. Also, it is impossible to anticipate future developments in statistical techniques or other scientific advances. Data from important health studies should be made available so that interested scientists can try their own analyses on the data, and so that statistical and scientific advances developed in the future can also be applied.

I recommend that data from major health studies be provided to scientists for independent analysis at their own expense. I propose that the data be made public in this way after the initial report is issued, and that it be provided at a moderate price reflecting the actual cost of computer formatting.

Now, as regards academic freedom. Unconscious and conscious desire to please the supervisor, and the supervisor's desire to protect the institution can lead to suboptimal scientific performance. This problem is particularly serious in hierarchical research settings such as those found in the Government where agency loyalties can conflict with scientific integrity. I believe that the appearance and possibility of inappropriate influence can be minimized in Government research, in Government-funded research, and in industrial research if formal policies are articulated and practiced by example by institutional leaders. These policies must firmly establish that scientists have the right and the responsibility to exercise full academic freedom. That is, scientists are to act in a manner fully independent of all nonscientific policies or interest.

This policy on academic freedom should be articulated clearly by institutional leaders at regular intervals, and should be followed by intermittent inquiries permitting confidentiality. Diverse viewpoints should be consciously encouraged. In occupational, environmental, and public health science, as in so many other settings, diversity is strength and tolerance for diversity must be cultivated.

In summary, governmental laboratories, Government-funded efforts, and industrial efforts are pivotal in occupational, environmental, and public health issues. The academic freedom of scientists and scientific quality can be assured by sensible programs of peer review, by publication of data, and by support of intellectual diversity in the research facility. If these things are not done, if academic freedom is not guaranteed, veterans will never receive the full measure of justice, nor will our Nation be able to adequately meet the occupational, environmental, and public health challenges of the future. Thank you.

[The prepared statement of Dr. Albanese appears on p. 117.]

Ms. PETROU. Thank you.

Dr. Kahn.

STATEMENT OF PETER C. KAHN, Ph.D., ASSOCIATE PROFESSOR OF BIOCHEMISTRY, DEPARTMENT OF BIOCHEMISTRY AND MICROBIOLOGY, RUTGERS UNIVERSITY

Dr. KAHN. Thank you for the opportunity to appear here today. In testifying, I wish to emphasize that I do so as an individual, speaking for myself rather than as a representative of my university or any other organization.

We are asked to address many questions today on the directions of future research into herbicide exposure and veterans' health, all of them complicated. There is not time to discuss any of them in depth, let alone all of them. The best I can do is to comment on a few and to make myself available to be of assistance both today and hereafter.

The Institute of Medicine's Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides has done an honest, workmanlike job. Having attempted my own literature review over the years, I have a good idea of just how hard it is to make sense of a bewildering array of often conflicting studies in a wide range of fields. I say this to emphasize that whatever criticisms I have of their report are minor and should not be blown out of proportion.

One of the committee's principal conclusions was that assessment of exposure to herbicides is the weakest link in the epidemiological work done on veterans to date. Fully five of their six specific recommendations concern the rigorous identification of exposed and unexposed groups of people and, among the exposed, establishing the degree of exposure. They are right. Unless this can be done, no valid health study is possible, for misclassification errors will obscure any real associations which may exist between exposure and disease.

Much work in the field has suffered from this problem, especially work on veterans. The realization of the need for good exposure assessment, in fact, motivated most of the studies in which I have participated, going back to 1981 when planning for New Jersey's project began. Given the limited resources available to us, we felt an exposure study would be the best contribution we could make. The measurement of TCDD levels seemed a reasonable approach at the time, so that's what we did.

I mention this to emphasize that although I participated in the development and validation of the methods currently in worldwide use to measure blood serum dioxin levels, I agree fully with the committee's recommendation to develop exposure data based on a broad range of historical records from the war. We advocated exactly such an approach in our paper back in 1988. The best work in this area to date, by the way, is certainly the Stellmans'. Praise should have been heaped upon them for it, instead of the vilification which has more often been their lot.

Blood measurements do have a role to play, which the committee point out, as an adjunct to and possible validation of records-based exposure estimation. They are right also in noting how thin our understanding of dioxin toxicokinetics is. This means we have little knowledge as to how variable the excretion rate may be from one person to another or whether women's bodies handle chemicals of this sort as men's do, although we do know something about lactation. There are other unknowns as well whose penetration is necessary to the fully effective use of the method for human benefit. I have, in addition, some detailed technical suggestions for which this short presentation is not the appropriate forum and which we could take up later.

I disagree with the IOM Committee on the clinical use of blood serum measurements. They are no different from any other labora-

tory test which might, or might not, guide physicians in diagnosis and treatment. It is true the test is expensive and time consuming. So are many others—a detailed immune function screen, for example. It is also true that a negative answer, i.e., a low current level, leaves one hanging, for one cannot know from such a result whether the patient always had a low level or whether it dropped back to normal in the time since the last exposure. Like any test, it depends for its clinical usefulness on the physician's knowing its strengths and weaknesses.

If this means educating doctors about it, so be it. That done, it should be the physician's and patient's joint decision, and if they decide it would be useful, the VA should pay for it whether or not the referring physician is a VA doctor. There are both moral and practical reasons for the VA to do so.

With respect to archiving samples and compiling clinical data from veterans who present themselves at VA facilities—the Agent Orange Registry, for example—I agree, there is little to be gained in the absence of a clear study design, and the data compiled without such a design can be, and have been, put to pernicious use. The General Accounting Office's scathing comments some years ago on quality assurance in data entry to the registry are pertinent here.

In order to develop methods of reconstructing exposure from military records, it will be necessary to rejuvenate the Joint Services Environmental Support Group (ESG). Years ago it became expert in sifting records and will certainly be needed to do so again. It has fallen on hard times, though, and will not be able to do what will be needed without an injection of money for staff and facilities. Clear and continuing administrative support from the Defense Department will also be needed for the ESG and for other of the IOM's recommendations.

The IOM discusses briefly the usefulness of research in Vietnam. It would most certainly be helpful, and research cooperation between that country and the United States already exists. I suggest it be expanded both within the United States and to include staff from the International Agency for Research on Cancer, an office of the United Nations. They, too, have significant competence from work in Vietnam.

Finally, the history of the Agent Orange controversy has been contentious, to put it mildly. For this reason, I cannot agree more strongly with the IOM's recommendations that all new work be organized, conducted, and evaluated by non-Federal entities. Above all, keep the VA out of it, and, with one exception, keep the CDC (Centers for Disease Control) out, too. That doesn't mean there aren't good VA scientists who could compete in a request for proposals, but we can take that up later. Likewise, the Agent Orange Working Group, if it still exists, should simply be abolished. This is not the place to rehash a sorry history, but if any of these agencies have significant roles, the public will not accept the results, and many scientists who have a great deal to contribute will have nothing to do with it.

The exception in the case of the CDC is the dioxin lab. It is a good lab. In fact, it is among the world's best. While I often disagree vigorously with their interpretations and presentations of data, I have never had a reason to question the quality of their

measurements or their honesty in presenting them. The lab could well be useful in doing body burden measurements. There are other labs in the country which should take part as well.

As a country, we have treated veterans shabbily in many ways, the Agent Orange controversy being but one of them. By failing to do the necessary research years ago, we brought discredit unfairly onto science and onto scientists as a group. We can't afford that, for if science is discredited, good people will not go into it and our civilization will suffer. We have weakened our democracy as well, for faced with the spectacle of the Agent Orange controversy, people lose faith in our governing institutions. We have a chance now to redeem some of that but only if we do it with vigor, steadiness of purpose over the long-term, and intelligence. Thank you.

[The prepared statement of Dr. Kahn appears on p. 120.]

Ms. PETROU. Thank you.

Dr. Arnold Schecter has arrived, and I want to introduce everyone to him and to fill him in on what we're doing at this point. We are having an informal staff forum so as not to inconvenience this group one more time. There will be a transcript and a record. We are going alphabetically and taking the statements first; then we will all talk.

So, Dr. Schecter, please proceed.

STATEMENT OF ARNOLD SCHECTER, M.D., PROFESSOR OF PREVENTIVE MEDICINE, HEALTH SCIENCE CENTER, STATE UNIVERSITY OF NEW YORK AT BINGHAMTON

Dr. SCHECTER. Thank you. I would like to ask that the documents I gave you be entered into the record: the presentation for the IOM NAS, December 8, 1982, which I sent you previously, was an up-to-date summary of our scientific knowledge at that time; the specific testimony I prepared for today; and the press release which is a very short form. Thank you for inviting me here. I am a Vietnam-era veteran of the U.S. Army Medical Corps. I am a physician who works full-time on Agent Orange and dioxin research, and I believe, for better or worse, that I am the only physician coordinating Agent Orange studies in Vietnam.

We are coordinating Vietnam-based studies for a number of reasons. After working with the Massachusetts Agent Orange study, where we determined that we could find ground-based as well as Air Force veterans with elevated TCDD in such a pattern that indicated exposure to Agent Orange decades ago, we went on to the Michigan study and also found that in a small percent of Michigan Vietnam veterans, we could find elevated dioxin levels of a pattern characteristic of Agent Orange exposure several decades before. In the Michigan study, we also learned that all Americans have higher levels of dioxin-like chemicals, that is the dioxin-like PCBs, than had previously been suspected—all Americans, not only veterans. We also identified for the first time dioxins in the semen, which we did because we were interested in male-mediated adverse reproductive outcome and we were following the suggestion of Maureen Hatch that dioxins in semen might provide a mechanism for male-mediated adverse reproductive effects.

Why are we working in Vietnam if we want to find out something useful for American veterans? There are two reasons. One is

we want to know environmentally where dioxins from Agent Orange got into people exposed to Agent Orange. Agent Orange, a unique mixture, was sprayed in Vietnam only. There were 17 million Vietnamese living in the south of Vietnam; they did not serve 1-year tours of duty—they are for the most part people who have lived continually in the area. We are easily able to find Vietnamese living in Vietnam with fat tissue, blood, or milk levels of dioxins which are elevated in a pattern which is consistent with Agent Orange exposure and intake. We believe that Vietnam uniquely provides us with a laboratory where we can identify very large populations of men, women, and children exposed to Agent Orange, including the 2,4,5–T, the 2,4–D, and the dioxin contaminant, and whatever else uniquely may have existed in Vietnam whether it be chemical, viral, bacterial, or other exposures.

Also in Vietnam, uniquely, there is an organization set up by the Vietnamese government which has the ministry of Health, Agriculture, and other ministries known as the 1080 Committee to study the consequences of chemicals used during war. In essence, this is an Agent Orange and dioxin study group which, for the most part, funds local Vietnamese efforts but also very much welcomes international efforts. We have worked with them since 1984, and my colleague and predecessor, Dr. John Constable, began work funded by the U.S. Government in 1970 and again in 1973.

Vietnamese women, I might point out in passing, have had the world's highest dioxin breast milk level ever measured in the world today and the highest dioxin level actually measured, not extrapolated but measured, from Agent Orange exposure. These data were from the work done by Dr. Bowman at Harvard University with the first ever measurements of dioxin in human tissue. When we replicated from archive samples, we found the same dioxin levels that he reported from those samples still available. Not all samples were still available.

We would strongly urge American research be funded in Vietnam as well as in the United States because it is very easy to find a population there exposed to higher levels of dioxins for long periods of time. It is also possible, unlike the United States, to find a control population with extremely low levels. When we presented our human tissue findings to the World Health Organization as to dioxin levels in milk and in blood, it appears that Vietnam uniquely is the only country in the world documented to date with higher and lower levels of dioxins by geographical regions. The north of Vietnam is like a preindustrial country with very low dioxin levels, whether they are the dioxins from industry—paper and pulp mill, municipal incinerators, pentachlorophenol—or the dioxin of Agent Orange. In the south of Vietnam, with the exception of the elevated dioxin from Agent Orange, the South Vietnamese are more like us in terms of dioxin levels.

In addition, who should do the research and how should it be done? I think at this point, as a Vietnam-era veteran advisor to The American Legion and having conducted two State (Massachusetts and Michigan) Vietnam veteran studies—I think there is not credibility at this point, whether for good or bad, if the Federal Government does the studies. Medical schools, universities, schools of public health, and independent research organizations, such as

the one that Dr. Stellman is affiliated with, can do an excellent job. We traditionally do. The number of Nobel Prizes won in physiology and medicine by the American university-based research workers is outstanding worldwide.

I would urge that whether the NIH (National Institutes of Health) funded research, whether the EPA (Environmental Protection Agency) funded research or not, let those of us who work in universities and medical schools try to solve the problem as to where Agent Orange exposure actually led to elevated levels in people's bodies, in American veterans and our former allies in the south of Vietnam, and what levels of dioxins cause health consequences. I think the current literature over the past 3 or 4 years has shown without any doubt that dioxins cause similar health consequences in humans as in laboratory animals, and, at least for certain biochemical endpoints, humans and laboratory rats are remarkably similar in the sensitivity we have. We are not an insensitive species, we are also not the most sensitive species; we are not guinea pigs, but we're not hamsters—we're not at the opposite ends of the spectrum.

There is one other thing you might want to consider. President Nixon did something remarkable when he waged war on drug abuse. He established a Drug Czar and a Special Action Office for Drug Abuse Prevention, SAODAP, headed by Dr. Jerome Jaffe, formerly a professor of psychiatry at the University of Chicago. That office did, in fact, fund cutting edge research and move the field forward. It was part of the Executive Office of the White House and functioned in a remarkable manner.

I think we are closer to getting answers but we also have a time limitation. With a half life of the dioxin which contaminated Agent Orange being somewhere between 5 and 12 years, somewhere in that range probably, and probably with a bi-phase—two-phase rapid diminution initially and then a slower excretion from the body later on—I think that we are fighting time. If we don't go in now, we are not going to get the answers because we won't know who was exposed despite the elegant research of the Stellmans on exposure indices.

The last thing I would say, and here I speak as a Vietnam-era veteran of the Army Medical Corps, the Federal Government is, quite rightly, spending large sums of money—I've read between $10 and $100 million a year—to solve the vexing issue of the MIAs/POWs. I would remind the Senate that there were 2,200 MIAs/POWs and I think there are about 1,600 unresolved cases at this time, and probably less, for Vietnam. There were 3 million Americans who served in Vietnam and who were potentially exposed to Agent Orange. They have families, they have spouses, they have children, they have fathers and mothers. Let's not forget that 3 million and focus only on the other problem area. Let's not forget the potential exposure of our veterans to Agent Orange. And let us fund with a reasonable amount of money extramural university medical school research projects to solve the question as to where exposure occurred in our veterans and where it didn't occur—we may be able to reassure many veterans, if not most—and what levels are of concern and what can we do about it. Thank you.

[The prepared statement and referenced documents of Dr. Schecter appear on pp. 123 and 132.]

Ms. PETROU. Thank you.

Dr. Silbergeld.

STATEMENT OF ELLEN K. SILBERGELD, Ph.D., SENIOR TOXICOLOGIST, ENVIRONMENTAL DEFENSE FUND, PROFESSOR OF EPIDEMIOLOGY AND TOXICOLOGY, UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

Dr. SILBERGELD. Thank you very much. I am not going to read my testimony. There is a complete copy of my testimony on the table outside. Some of you may have picked up a copy that is Xeroxed on nonrecycled paper and those copies are incomplete and mixed up. The copy that is Xeroxed on recycled paper I am happy to say is complete and in the correct order. So, if you want to look more fully, that is the one you should make reference to.

Ms. PETROU. We will get full copies of that to anyone who needs it.

Dr. SILBERGELD. Thank you. I would really like to focus on two points from my testimony, because many of the other points that I touched upon and intended to discuss have already been mentioned, in much the way I would hope to express them, by the previous speakers. I would like to focus on the issue of exactly what kind of research we should be doing at this point to answer this central question: What are the likely health effects that we could expect to see in Vietnam-era veterans? My answer to that question will be a little bit different from what you've heard so far because the research that may help us understand that may include groups of people other than Vietnam veterans.

It is a very well-known fact in biomedical research that we can gain insight from a variety of sources and that we should not restrict our focus to the narrowly defined group of concern, because often other sources of information give us an opportunity to understand critical issues in the very way in which they present themselves. For instance, the NIOSH Dioxin Registry of industrially exposed American workers is probably one of the richest and best conducted epidemiologic investigations of dioxin. I would note that it was also conducted by U.S. Government, so it is certainly possible for Government to do excellent and exceptional research. From that study, in fact, we have gained important insights that can be used scientifically in a highly interactive and fruitful way to help us understand the results that we have obtained to date from the Agent Orange studies and the Ranch Hand studies, and also to frame, I think, the critical research questions for any further research that may benefit Ranch Hand and other veterans from the Vietnam era. So let me say, first off, let's not take a narrow view on this topic.

Any of the studies that have been done to date on the Vietnam-era cohorts have been, in my opinion, scientifically poorly designed, with inappropriate questions framed, and, therefore, not surprisingly, inadequate answers found. Even in those instances where relatively reasonable research designs were applied and some possibility of reaching some conclusion within the design was possible, I have been struck, as I think many have, at the disparities be-

tween the conclusions of the studies and the interpretations that have been made of those studies by many Government officials.

I would strongly endorse Dr. Tollerud's point that increasing the availability of the fundamental data set will allow the scientific community and the public at large access to the same information which others have used to draw conclusions that they have wanted to draw at various points throughout this process.

The kinds of research issues, in my opinion, that are extremely important for us to come to an understanding about health effects at this point are as follows, and they are perhaps slightly different from the ones that you may have heard before.

I do not believe that further epidemiologic research, particularly within the constraints of the Vietnam-era populations, are going to add to our understanding of the cancer risks of dioxin. I firmly believe that the followups being conducted of the industrial cohorts by IARC, the International Agency for Research in Cancer that Dr. Kahn referred to, and by the National Institute of Occupational Safety and Health, together with a redirected and refined examination of certain special populations, such as Seveso—two days ago I was in Italy listening to the latest report of the data on the cancer risks in the Seveso population—will inform our information much better with respect to the nature of the cancer risks which we may expect to see. We can then take that information and apply it in somewhat different designs, and I suggested in my testimony perhaps it is time to evaluate the utility of case-controlled studies within VA and other registries, rather than the classic cohort design which has been the standard method of investigation of the Vietnam-era veteran populations to date.

The critical issues that still remain extant in our understanding of the nature of the health effects and whether we use the Vietnam veteran cohorts or others to inform our understanding is an issue, but these are qualitatively the areas where I think we are still incomplete in our understanding. One is the interaction of early dioxin exposure. Here, I think we have to rely on absolutely all the information we can gain to determine what that exposure is. We should not be evaluating body burden measurements versus historic analysis of data. Any epidemiologist should try to accumulate all sources of data and integrate them to the best extent possible, not to weigh one against the other.

We need to understand what are the long-term sequelae of exposures, particularly as two critical systems in the body age—that is, the reproductive and the immune systems. I would hypothesize that there may be revealed the consequences of early hits on critical aspects of those two systems that are stressed or depleted as the body ages.

In terms of systems, understanding the area of neurologic and neuroendocrinologic toxicity and Agent Orange and its constituents remains still the area of our least complete knowledge. I was disappointed that the IOM panel took a very restrictive point of view in terms of the information they chose to review to inform their own qualitative judgment as to the hazards and toxicity of these component chemicals. They omitted a great deal of important and, in my opinion as well as the opinion of EPA and others, extremely valuable relevant studies on cohorts that have been exposed to

dibenzofurans such as in Taiwan and Japan, and the large body of extremely important experimental research. These are particularly important with these endpoints of neurologic and neuroendocrinologic toxicity, because we really don't have that much information otherwise.

I think it is important to note on a date of the unveiling of the monument for the women who served in the American forces during the Vietnam era that we have overlooked examining the health risks of Agent Orange for women. Again, we need to examine this on the basis of wherever we can get this information, be it Seveso, be it Yusho, be it Yucheng, to incorporate that into well-designed studies of the potential effects of exposure on women.

I certainly endorse many remarks within the IOM report about adding to our armamentarium of exposure assessment all the techniques of molecular biology which may give us further information on past or ongoing cell level exposures to this chemical.

And finally, let me state again that at this point I think case control studies through a linked VA hospital system, and hopefully through a national health care system, may allow us to collect on a timely basis surveillance information on the incidence of health effects which can then be examined as to the relative association with past service in Vietnam. With respect to the structures and processes for conducting this research, I certainly agree that the past record makes many people inside and outside Government place little confidence in the continuing process that has occurred.

But let me add another problem which troubles me a great deal, and I would admit myself to be a participant in this particular problem; and that is, wherever we place the resources for doing these types of research, be it within Government, be it within universities, be it within novel structures, we still have a major problem in obtaining critical oversight and review. First off, the review process must be thorough and far-reaching; it must begin at the beginning and carry through to the end. Too often I have been asked to serve on expert panels which deal with a product that was flawed from the outset. It is impossible to bring valuable insight or criticism to fellow researchers who have conducted a study with a flawed design. Unless the review process begins at the beginning and carries through to the end, it is of relatively little value.

More fundamentally, these review processes seem to involve the same people sitting on the same committees reviewing the same types of issues from different perspectives, and here I say I have been part of that closed circle as well. This is an issue I think that extends beyond Agent Orange and is a very troubling aspect of the whole issue of expert advice to Government, including the OTA system to Congress. It is something to which Congress needs to give very deep thought. It goes to the issues that Dr. Albanese raised about opening the process and searching for the broadest possible representation.

Sometimes the National Academy of Sciences and the Institute of Medicine seem to fear the very nature of the issues that they are charged by Congress and the agencies to deal with; that is, these are controversial issues of importance and interest to many sectors of American society. I say that their reaction is one of fear in some instances because they seem to want to deny the very vitality of

the controversy which has brought the issue to their attention for resolution, and they attempt to search high and low to find persons who in their perspective are untainted by that controversy. I have to tell you it has been my experience that most people who are knowledgeable about an issue have at some point probably taken a position on the issue.

So, by establishing this impossible criterion of purity of utterance, one then excludes for availability most of the people who have any expertise in the subject. With due respect to Dr. Tollerud and his colleagues, I think that limitation did, in fact, affect some of the conclusions of the IOM report, and I have detailed some of them within my testimony. But this whole process of scientific review and expertise is one that would repay investigation and assessment by the Congress, because we are all increasingly dependent upon it as we deal with ever more complex issues for resolution. Thank you.

[The prepared statement of Dr. Silbergeld appears on p. 165.]

Ms. PETROU. Thank you.

Dr. Stellman.

STATEMENT OF JEANNE STELLMAN, Ph.D., ASSOCIATE PROFESSOR OF PUBLIC HEALTH, COLUMBIA UNIVERSITY

Dr. STELLMAN. Being the last is both good and bad. Many of the points I wanted to make have been made, which is interesting in that there seems to be a uniformity of some conclusions here. I am speaking today on behalf of myself and my husband and am not representing the International Labor Office of the United Nations where I am serving as editor of their Encyclopedia of Occupational Health and Safety. Our full comments are submitted separately.

I am going to try to just dwell a little bit on what I see as what is left to us as the aftermath of the NAS IOM report and the report done by the VA Agent Orange Task Force, the membership of which is not clear from reading the report. We agree with the preponderance of recommendations made by the IOM, but have made a series of our own recommendations.

The first deals with the whole question of what we have taken to call "mega-science," the study designed to answer all questions for all times with a single report. Anybody who has read today's paper sees the other IOM report that has come out on the women's health study. I think that much of the conclusions of the IOM with regard to that potential boondoggle applies very much to what we've seen in practice with Agent Orange, where epidemiology studies have been conceived of as being able to answer all questions. The nature of epidemiology is such that that is simply not possible to do.

Epidemiology is not a science in which one goes out and constructs the events; it is a science in which you try to reconstruct events for an experiment that has been done either by nature or by politics upon a population of human beings. This means that, since we're talking about inexactitudes in both exposures and outcome measures, it is not just the exposures that are inexact, but that we have to try to poke at the problem from a variety of different perspectives.

That, by and large, means that we need to have many people think about the subject, many people formulate hypotheses which are biologically plausible and approach them with different measures. It is only after a number of studies have been done that we can draw some sort of consensus, that a group of people knowledgeable can sit—and they don't necessarily all have to be scientists, incidently—and evaluate whether or not consensus and replication has occurred. These are inexact measures and, therefore, they have light error bands. The way to narrow the error bands is to do the work over and over. It is not very different from measuring physical constants. You have to do fewer measures for that and you are more clear about what the parameters are.

In addition to the politics of Agent Orange and Vietnam veterans research that have plagued us for more than a decade, there has been this mega-science central control of all information that has almost been as big a plague in my estimation as the political influences on science. Therefore, our first recommendation is to avoid this mega-science trap.

Our second recommendation is to agree very much that specialized subgroup studies are needed. I don't necessarily agree with Ellen Silbergeld, if I understood her correctly, that Vietnam veterans may not be the best place to look. I agree with her very much that we have to support research and look at studies of populations which have similar exposures or relevant exposures, but I think that within the Vietnam veteran group, our best estimates are about 20 percent of the people who served in Vietnam have the potential for telling us a great deal both about mechanism and about cancer.

Our own analysis of the data available through the Agent Orange Veteran Payment Program, which is not in our testimony but we can provide this, has shown very unusual cancer patterns. Just yesterday at a meeting in Baltimore I heard some NIOSH results in which one of their studies has found buccal cavity cancer which they don't understand. I was sitting there thinking, "Well, that is exactly what was found in Ranch Hand and that is exactly what we are seeing." So, perhaps there is something there.

So, while I believe that we have to look at all populations, I think Vietnam veterans are a fruitful source of information. The Army Chemical Corps has been mentioned as a special group, the nurses in Vietnam have been mentioned as a special group. I draw your attention to the fact that the National Cancer Institute has published a study on scout dogs that served in Vietnam and that have been found to have elevated levels of testicular cancer. Every one of those scout dogs was led by a soldier in a scout dog handling unit. That is another potential group for looking.

The fact is that to date the one specialized group that has been chosen has been the Ranch Hand group and it is not at all clear to us that the Ranch Hand group was ever the one, as it is constructed, to be given the highest priority. We don't necessarily agree with some of the IOM's conclusions on the Ranch Hand. We think that the study should be pretty much shut down as it is now and that the data that has been collected in the past be consolidated, made useful, made more easy to understand, and made

available to external researchers who can evaluate the voluminous amount of data.

We have never been convinced that the original study design made a lot of sense, that the original Ranch Hand group was actually properly identified. It was not drawn from military records but from a volunteer association, and there has never been complete followup. The exposure measure has always been ludicrous. To take the total amount of Agent Orange dropped in any 1 year and divide it by the number of people in any one job category is just silly. Every year this group has dutifully presented its results to the Congress which has never asked it any real questions.

I think it would be wrong simply to continue spending so much money on a study that has never proved its merit. I think it is time to stop and look at what we actually have there before going on. Dr. Albanese, in fact, has been able to draw some interesting data out of it. I suggest that we open that data up to other people to look at as well.

I also completely agree that it is necessary to have external advisory committees, both of scientific but also nonscientific advisory committee members and people who are technical people from the community at large to participate with the researchers. Many aspects of the CDC research, for example, really suffer from a lack of good common sense and knowledge about what happened in Vietnam. Restricting tours of service to 1 year, restricting the people who could serve to E–1 to E–5 military levels in essence guaranteed that we look at the least exposed, not the most exposed. We need to have people such as Dick Christian from The American Legion, people who have worked very hard with the veterans, technical people from the communities at large to serve continually to provide good common sense and good input and good cheer to the people who are trying to do the research.

Another reason that I believe it is necessary to continue to look at Vietnam veterans as a group, especially for cancer research, is that we must continue to explore the relationship between exposure to herbicides and exposure to combat. It is very clear that stressful conditions, be they at work or the work of a soldier at war, can alter the effect of a toxic substance. By failing to take combat into account, as has been done through many of these studies, we may be missing one of the key factors in what may be producing the ill health of veterans.

We also strongly disagree—I guess I have to say that—strongly disagree with the recommendation taken that a registry of all Vietnam veterans be conducted. I think that is a hugely expensive undertaking that would not produce much of value. In working with the Eastern District Court on the Agent Orange Veterans Payment Plan, we have had to collect 70,000 military records, and with the best of cooperation from the St. Louis Records Center, it is an awesome job to try to collect all those records. And what we would be doing would be to expend huge amounts of money in collecting the records of people who were largely not exposed to anything and many of whom were not even in Vietnam or close to it or served on board ships. The presence of a Vietnam service medal does not indicate that you were any place near spraying. It is a huge project.

Instead, in our testimony we offer as an alternative that we develop a uniform way by which military records are extracted and that we develop a data base based on the extractions, so that we don't have to extract the same record more than once; that either through the resurrection of the ESG—well, ESG is actually alive and well—the expansion of the ESG or through a cooperative program with the St. Louis Records Center we develop a mechanism by which researchers can have easy access, providing of course for confidentiality, to the records, that uniform records be extracted, and that the data bases be collected so that we don't do it more than once.

But, again, we strongly think that looking at all the Vietnam-era veterans is going to have very, very limited payoff. If one feels that one has to go ahead and do this, although I can't see why, I strongly urge that a pilot study be done first before we invest millions and millions and millions of dollars and put off the whole process for another year or two while this gigantic undertaking is begun.

Finally, it was of course very heartening to hear people talk about the historical reconstruction of exposure opportunity from military records and to have that be validated both by the IOM and by members of this panel. We would like to say that we have, and the Government has paid for through its funding of the CDC's work and its contracts with ESG, collected of huge amounts of data on troop locations.

I very heartily agree with everyone here who has said that it is a fruitless and negative effort to pit one kind of exposure measure against the other. They are all complementary. We don't have to be cheerleaders for any one side in exposure methodology.

I would urge that, again, a means be developed by which this is kept an open process. I would like to remind the Senate that we only obtained these records because the judge in the Eastern District Court was forced to file a Freedom of Information Act inquiry to get the records from the CDC. It is only because of inside information on what records to ask for that the judiciary branch of our Government was able to obtain these data from the executive branch. This is a frightening piece of history to me and one that we should see not be repeated.

We stand ready to try to open up this data base and to do the necessary work to both validate it and to develop more precise knowledge of where it is good and where it fails. We believe that these written records are a valuable supplement to whatever else exists.

We wish to thank you very much for this long awaited opportunity, and we endorse very much the oft repeated sentiment that this work be allowed to be continued on an independent basis.

Thank you.

[The prepared statement of Dr. Stellman appears on p. 178.]

Ms. PETROU. Thank you.

There seems to be one point of agreement, and that is not to pit exposure measures against one another. I think that each one of you has experience in that area. Maybe it would be nice to start off talking about whether or not measuring exposure is as much a problem in occupational studies and Seveso and other places as it is in Vietnam veterans. One of the NAS recommendations was to

develop more biomarkers and better biomarkers, so the question is, how do we get there? Anybody who wants to comment on that can start.

Dr. Silbergeld. And anybody can just jump in.

Dr. SILBERGELD. In many respects, of course, it is easier to both develop and to validate exposure measures for the occupational cohorts and for exceptional situations such as Seveso. That is because in many of the industrial groups, of course, you have work records as well as descriptions that can be extremely fine structured as to the actual job and working conditions in which various members of the cohort have been involved.

Sometimes it is less clear the more one gets information, but in certain circumstances it can be very useful. When you have an incident like Seveso which occurred at a discrete moment in time and for which serial samples have been taken—of the environment, of food, and of human tissues—over the period from 1976 through the present, then you have a rather unique archive of historical records, both biological as well as descriptive, which may be called upon.

But I think that there are some very important variables to keep in mind so that one does not look to the biology or the chemistry as a magic solution to the problems of actually having to do the kind of work that Dr. Stellman has done. I don't think the biology is ever going to extricate you from that obligation of understanding the situation, which means of course involving the people who were there, and obtaining as many of the descriptive records as one can.

One is that there are clearly interindividual differences in both the handling of these compounds as well as in the likely response. Particularly if we are going to go to cellular and genomic markers of response to TCDD, which is an extremely hot area of research right now, and we are involved in looking at gene expression in response to TCDD in human and other cells, then one immediately is involved in understanding the extent to which these alluringly precise but highly variable events may occur and the effects of individual to individual variation upon their expression and detectability.

The other thing is that there are major events over the lifetime which are clearly going to influence the compartmentalization and the total amount of TCDD within available body compartments. We know that over the lifetime changes in body composition, the mobilization and accumulation of the fat compartment will have major impacts upon what we measure in either a biopsied sample of the fat compartment or a mobilized amount of fat into the blood stream, which is what CDC has generally been doing. Particularly, as has been pointed out, as time goes on and particularly in cases where intercurrent disease may also affect these physiologic parameters, our ability to generalize or to utilize the biologic data as a way of helping us out of the complexities of classical exposure assessment, be it within the workplace or in these circumstances of the military workplace, as Dr. Stellman so well describes it, again I think caution us against an either/or or hoping that the biology will save us from the hard work of doing really comprehensive exposure assessment.

I think that the biomarkers may, in fact, help us understand something in the variations of response. For example, within the Seveso population, we now know that there seems to be about a sixfold increase in certain types of lymphopoietic cancers. But not everyone who was similarly exposed is expressing this response. Now, one of the interesting things that is emerging in some of the populations where we can do this, such as the Japanese population and Seveso, is a strong sex dependence of the response. For instance, women seem to be protected against breast cancer in Seveso but are much more at risk for some of the gastrointestinal cancers. So that gives us another reason to be very careful about simplistic interpretation of markers. On the other hand, the possibility exists that the markers might not only help us understand exposure, but also delineate the differences in response.

Dr. SCHECTER. I wonder if I could also point out some of what goes on in occupational medicine today which Dr. Jeanne Stellman has presented previously. When I practice occupational medicine, when I see a patient who walks into my office, I don't have a specific biomarker of exposure. What I have is the fact that he or she worked in an asbestos laden environment for a certain period of time, or that the person worked in dry cleaning and was exposed to chlorinated solvents.

Having a dioxin measurement is very useful, but that is not the way we normally practice medicine nor the way we normally do research in occupational medicine. It is nice to have this $1,000 to $2,000 test, and it would be nice to have even more sensitive markers, but you don't really need that usually in the real life practice of medicine. For that matter, if you are talking about compensation, you know that if there is exposure, you know that dioxins are definitely promoters of cancer; that is, they promote cancer if a person has been exposed to it.

Again, I would agree with the genetic differences that we find. We have a family with three children. When we go to the zoo, only one of our children breaks out with an asthmatic attack. The exposure is the same, but the genetics, even between my wife, myself, and our three children, is different. So there are genetic differences. Most lung cancer in the United States comes from cigarettes; most people who smoke cigarettes do not get lung cancer. On a population basis, the rate goes up proportional to your exposure and your genetics.

But let's talk about where we can get the answers. The molecular side is very lovely science, but one nice thing about doing epidemiology studies is to have large populations with high exposures and low exposures. It is also nice if you have men and women and children, because we know that children have cognitive and behavioral problems when their mother is exposed before they are born; the children later have problems. This has been shown by Walter Rogan in two different populations, as well as by Peterson in human and animal studies.

Vietnam now has about 35 million people living in the south of Vietnam, and about 35 million people living in the north of Vietnam. The people living in the south of Vietnam have a much higher dioxin exposure than the people living in the north. Unfortunately for the Vietnamese but fortunately for us, if we want to get

answers about exposure and health effects on our veterans, Vietnam offers a unique laboratory to get answers much more quickly than we can get elsewhere. Seveso has a few thousand people and they are of great interest, as does the Yusho, which has 2,000, the Yucheng, where I saw poisoning in Japan and Taiwan—about 2,000 exposed people to higher or lower exposure in each group—and a few thousand in Seveso, which of course is a place to be studied. But compare 35 million people with higher exposure and 35 million with lower.

I agree with Dr. Jeanne Stellman that these mega-science projects are ridiculous usually. If you focus on small, targeted questions, you can get small, targeted answers on reproductive effect, immune deficiency, effect on women, effect on reproduction, cancer, and other outcomes. I think we have a way of doing it and I don't think we should focus on minutiae.

Dr. KAHN. Could I jump into this one, too. We have done some work in trying to devise biochemical markers. It turns out to be very, very hard. I want to agree with Dr. Silbergeld, there is no dipstick, there is not even a DNA dipstick, as she commented when I made an aside to her.

I agree that the search for biomarkers should go on because it will teach us about the variability from one person to another. It is also going to give us a good deal of insight into biochemical mechanism. And above all, we need insight into biochemical mechanism. So I would support going out looking for biomarkers. It can be done in a series of small, investigator-initiated, rather tightly focused projects. I even have a number of ideas as to specific projects that could be looked at, which we can take up if somebody wishes to do so.

About the ability to generate cohorts of men who could be looked at, there are a number of useful things that could be done, some of which grow out of our experience in New Jersey, some of which grow out of what you have reported along with Steve in some of your papers. It isn't that difficult to find a few men who were heavily exposed in the field, which can be verified from their records. I am not now talking about Ranch Handers or the people who handled the spray. We have learned by interview techniques and questionnaires how to elicit sufficient information to have a feeling for whether a man was heavily exposed or not. Then you can go and back that up from the military record of that person.

Having found men who are exposed, you can then go to the unit rosters, because if that man was exposed, so was the next guy in the same unit. Even if they were distributed over 10 or 20 square kilometers on a particular day, they weren't always distributed the same way every day, and the chances that all men in a particular unit would be exposed if several of them are would be very high. The unit rosters exist; we've seen them, I've looked at them. So there are a variety of techniques where you can, as has been suggested here, bring to bear all the information that is available in establishing some credible, intelligent way of dividing people into those who were exposed and those who were not, and into varying degrees of exposure.

It is a significant burden to do that. But there are all sorts of things that can be brought to bear toward that end. I don't think

it is an insurmountable job and I don't think it is going to cost $50 million to do it, just to establish that information.

Dr. STELLMAN. If I could just give a specific numeric answer to what you were saying, asking about occupation versus Vietnam, I believe the Fingerhut NIOSH study had about 1,600 people in it. We have in the Agent Orange Veterans' Payment Plan about 70,000 claimants. Out of this, 85 percent passed a rather lax exposure test set by the judge. I would say that if we were being more stringent in looking for people who are highly exposed, somehow or other, even though this is a self-selected cohort, about half of these people I would consider would be judged highly exposed by almost any measure. These are the people who have some sort of disease or disability already. These are 50,000 people who were really gathered with very little effort.

Dr. KAHN. So if you are going to do case control studies, that is a good way to start.

Dr. STELLMAN. There are any number of potential areas. I think that what we learned from the Seveso, which is also another very small "n," is that it shows us what it is possible to do if you have a national or international will to do something. That is the major difference between Vietnam and Seveso—in Vietnam, we have many, many, many more people who were exposed and we studiously avoided doing the study; whereas in Seveso, they recognized the magnitude of the disaster and then set about trying to gather as much information as they could as rapidly as possible. One is an exemplary data base and one is a pitiful one.

Dr. ALBANESE. I think that historical reconstruction needs to be used along with the biomarkers. I think we have to pay a lot of attention to the operational circumstances of the exposure. I would like to suggest that we need to be more flexible with regard to our conceptual schemes. We need to think about body burden, but we also need to think about rate of change of body burden, dose-rate effects. Dioxin acts through free radical intermediaries. There is enzyme induction. So just like with radiation, you would expect dose and dose-rate effects. So, I think we need a broader conceptual scheme that would include details of operational exposure.

Dr. SCHECTER. On that point, there is one practical problem that we all face when we see Vietnam veterans, and that is, if in our clinical judgment based on our training and experience we feel that a dioxin measurement of blood or fat would be useful, how will it be paid for? I would urge that be considered and addressed. I would agree with the statements made earlier that the Centers for Disease Control have an outstanding dioxin laboratory, and there are others available as well.

It would be unfortunate if the IOM report and its criticism of weaknesses in the use of tissue measurements of dioxin resulted in the conclusion that payment for it should not be done unless it is part of a well-designed group research project. That would cause problems for the individual veteran who seeks a medical evaluation either at the VA or through private physicians. I would urge that some mechanism for payment for dioxin body burden or tissue analysis be considered. It can be very useful as can any one laboratory test, none of which are perfect.

Ms. PETROU. I've got tons of questions, but I am going to let other people ask some. But one question I have is, there has been the suggestion—CDC made it, and others have, too—that we don't have a good enough assessment of exposure to do studies. I know that many of you are working on exposure assessment. But I remember when the Ranch Hand exposure assessment was initiated that it was limited, but the best the Air Force could come up with, and they readily say that. They have improved it since then; they have seen problems with the original exposure assessment and have attempted to improve it. They still say it is not perfect, and I think many would agree with that.

I am not focusing on Ranch Hand specifically, but has there been a different standard applied to dioxin-related exposure assessments, particularly in epidemiology, than to other studies? There can be no perfect exposure assessment, I assume, in any area, even outside dioxin. Are exposure assessments in the area of dioxins worse than they are in other areas? If so, what can we do through exposure reconstruction modeling or other means to make them useful?

Dr. STELLMAN. As a little exercise, a few years ago I had a graduate student sit down with CDC's own studies of dioxins and just make a matrix of what it used. Many of its exposure measures were a matter of convenience. In one set of studies, the Trailer Park—where was that, Missouri?—Quail Run, they used number of years that you lived in a trailer; whereas for Vietnam, they set up a standard and published papers in which they were saying there were no correlations when, in fact, we obtained the data of their so-called validation study and found that the levels of correlation between their historical data, which of course completely matches ours because it is the same data, had a very high degree of correlation.

I don't think the question has really been tested. We have had the opportunity to actually look at their raw worksheets and their raw data sheets and we don't find a disagreement. What they were doing and what we've been doing were virtually identical, interchangeable. But what happened apparently in looking through these boxes of papers that The American Legion obtained in its lawsuit against the Government for stopping the epidemiology study, what appears to have happened is that one day they just stopped the analysis that they had been moving on. Using this historical data, they had quantified which units were exposed and which ones weren't exposed, their lists match our lists; and then one day the process just ground to a halt and this validation study was undertaken, and the people who were included in it were from the least exposed units, not the most exposed units.

I have never understood, nor do I actually want to understand, what happened in that. But, yes, there has been a different standard; and, too, there has been just an abandonment of what seems like a perfectly logical way of proceeding and using these records that were collected with great care. The methods which were reviewed earlier by the Institute of Medicine were found good, and then suddenly obfuscation and just stopping the project occurred.

Dr. KAHN. Could I add something to this? One of the things that we learned, and that was alluded to earlier by some of the other

speakers, is that it is important to consult the veterans, and the IOM did this in the course of preparing its report as well. For heaven's sake, they were there and we were not. As a scientist, I am perfectly capable of forming a judgment as to whether some specific thing that a veteran has told me is going to be of scientific use or whether it is not, but I need the input, because of the hundred things that a veteran may tell me, there might be three that are crucial and I have to know those three.

We did this when we set up our study. We had veterans who were knowledgeable of what happened in the field involved at the very earliest stages of conceptual formulation of the project. That involvement continued right through the design of how you handle individual veterans when they come in for testing and so forth. We had Vietnam veterans involved at all stages of it in various capacities. Without that, the rather slender budget and resources that we had would have gone nowhere and we would not have been successful.

There has been a notable reluctance on the part of the Federal studies to actually listen to what the veterans have to say. I would say there has been a kind of arrogance in assuming that we, the people with the Ph.D.s, know best and that anything that a veteran could possibly say is going to be a self-serving lie. Well, neither of those two statements is true. We don't always know best. We need the advice from outside, and the veterans don't generally lie. I think it is important that that be taken into account in formulating any further projects that involve them.

Dr. STELLMAN. I would like to reinforce that. In fact, if you go back and read the CDC papers and the Vietnam-era study, it literally says that you can't rely on anything that a veteran says, that they will lie, and that is why some of the stress results which are consistent throughout the country were rejected. Epidemiology and the reconstruction of exposure histories is only as good as the hypothesis on which you base them.

One of the reasons I believe the ESG data collection was so good was that it was run by the people who were in Vietnam and who collected the records. So they knew what they were doing. One of the hallmarks of the lack of using this record was that there was a continual cat and dog fight between people in Atlanta who didn't have any idea of how the military worked and people in the ESG who were the military and were retrieving the records. We have data from the CDC where they actually for a time were tracking enemy movements and calling them our own because they couldn't tell one from the other. So, I think that part of what has happened was a giant boondoggle in which the people who knew best were not listened to.

Mr. TUERK. I'll take a turn.

Ms. PETROU. OK.

Mr. TUERK. Sorry if I seem to grope along here. I am not used to asking questions in this room, in this panel, or offering my own opinions. I am not going to offer my own opinions today either. [Laughter.]

I'm not elected to anything; my opinions aren't particularly useful or salient here.

Dr. KAHN. You can tell us over lunch.

Mr. TUERK. Perhaps, though some of my opinions will be revealed by some of the things I say. I guess I would open up by saying that it is a little discouraging to hear the testimony that we're hearing today and to read the statements of today's witnesses. Obviously, we all wish science could tell us which veterans were exposed to which chemicals, and which exposures have caused which diseases. That would make our task easy. Certainly, everyone here wants to compensate those veterans who do, in fact, suffer service-connected injury as a result of their service in Vietnam. Unfortunately, studies like the NAS report says that 87 percent of the lung cancer deaths in the United States are caused by smoking. Yet we're proceeding to make decisions to afford compensation to people who may have smoked their entire lives based on service in Vietnam. I think that gives us all some pause, both on a staff level and, I know, from the standpoint of my Senator.

With respect to lung cancer, for example, VA has made a decision to service connect this disease to Vietnam service, and VA costs that decision, over 5 years, at $285 million, a cost that only represents the tip of the iceberg as we project out the compensation benefits to veterans and DIC benefits to veterans' survivors. And yet, having listened to this panel of distinguished scientists, I don't feel much more comfortable than I felt before that VA's decision is based on scientific criteria that we can rely on. I am sure that you, too, would like to see clear answers and bright lines generated by your work. But that's not the case—and perhaps it cannot be the case.

Some of the things said in our witnesses' statement are particularly notable. Dr. Kahn, for example, you said in your statement, "Unless this (exposure studies) can be done, no valid health study is possible." Since this can't be done, I can only——

Dr. KAHN. It can be done. I wasn't saying it can't be done.

Mr. TUERK. Since this, then, has not yet been done, I can only conclude that you would conclude that all of the studies that we see so far are not valid.

Dr. KAHN. More or less.

Mr. TUERK. OK.

Dr. SCHECTER. No, there are some. I would like to add—

Mr. TUERK. Just hold on for 1 second and then we will throw it open to the panel.

Dr. Stellman, for example, comments—obviously and accurately—that presumptions that are made with respect to exposure in Vietnam are faulty; i.e., an individual's service in Vietnam does not of itself, necessarily mean or she has been exposed. We all agree to that. Obviously, we're making policies here with respect to compensation issues that layer presumption upon presumption and, unfortunately, that is all we can do.

My first question, based on all this introductory commentary, and I would throw it open to all of you, is this: your objective is to find out at some point whether—to put it in very simplified terms—whether herbicides cause disease in humans. Do you think that it is going to be possible to come to any firm conclusions on that question that are more valid than those that have been arrived at so far within any timeframe that is useful to this Committee? Our goal here is not to find the answer for its own sake; our

goal here is to help veterans who need help by providing compensation and medical care. And if we get the answer to the causation question after affected veterans have all passed away, it won't have been very useful for us to have the scientific input. Boy, I was trying to be provocative and I think I have been. I see some hands raised.

Also, let me ask one other question, and this goes to Dr. Schecter's work particularly. Do you think it is ever going to be possible to come to conclusions different from those that Dr. Schecter and the Fingerhut study came to, namely, that very high levels of exposure to dioxin—Vietnam civilians who were rained on for years or the Fingerhut cohorts who suffered over 5 years of exposure—led to higher lung cancer incidences. Those findings aren't particularly relevant, it seems to me, with respect to the population that we're dealing with—service personnel who were in Vietnam for a period of 365 days, generally speaking. Will it be possible to ever come to conclusions with respect to a shorter timeframe? So, that is a two-part question, and I throw it out and hopefully we can get some discussion.

Dr. SCHECTER. I think we have some answers. Since you've cited some of our work, what we have found, No. 1, is that dioxins are extraordinarily persistent. We have found dioxins 36 years after German workers were exposed to them, we found them in Vietnam veterans between 20 and 30 years afterwards, and we're finding them in Vietnamese long times afterwards. In Russian women workers, their children, 25 years after they manufactured 2,4,5–T, which is a component found in Agent Orange, the children still have elevated levels from nursing and from transplacental passage. These are very persistent.

We have herbicide work, epidemiology studies on 2,4–D done by the National Cancer Institute, which show increase in cancer of kinds with which we are concerned. We have a number of studies—the Koretsuni studies from Japan showing certain types of cancer, the Fingerhut studies, the Seveso cancer studies, German workers, International Agency on Research in Cancer—showing cancer mortality after exposure to these chemicals. We also have studies which show that humans respond to those things looked at in Dr. George Lucier's laboratory, certain biochemical measures, at the same level of sensitivity as lab rats, which are an average laboratory animal, in response to these highly toxic chemicals. We see from the Yusho and Yucheng studies that humans respond in the same way that laboratory animals do.

We see from Walter Rogan's work at the National Institutes of Health that even with low PCB exposures—PCBs are similar to dioxins chemically and biologically—in North Carolina mothers, the children have measurable outcome. When the exposure is higher, not just average high for the United States but for the normal population, we are seeing problems in our children. In the Yucheng mothers, the rice oil poisoning with dioxin-like chemicals in Taiwan, we're seeing malformations, we're seeing fetal death, we're seeing babies with lower IQs, cognitive and behavioral alterations.

I think we have answers right now that are very useful for compensation. We know dioxins in 19 out of 19 animal studies cause cancer. Every cancer study done on dioxins in animals shows they

cause cancer. Whether it is by initiation or promotion is very interesting theoretically, but for the veteran and his or her spouse, that should have nothing to do with the compensation. The compensation, you can go from the science and put in the policy aspect and come up with a conclusion. But I think the science, to give you the answer, we know an enormous amount today.

Mr. TUERK. If I may, and I focused principally on lung cancer for purposes of my preparation here because that is the issue——

Dr. SCHECTER. But you have a number of studies showing lung cancer in exposed groups. And the other thing—your point is well taken, we teach our medical students that uranium can cause lung cancers, smoking can cause it, but the two together cause a much, much higher level. I think that is probably what we are seeing in veterans who are smokers who also were exposed to a powerful promoter, dioxin.

Mr. TUERK. I understand your point, Dr. Schecter. I notice as well Dr. Silbergeld's statement in her testimony that, "In the opinion of most scientists, TCDD is carcinogenic to humans."

I guess I would ask Dr. Tollerud, your volume does not come to quite such strong conclusions. Why is that? What am I missing?

Dr. TOLLERUD. What conclusions?

Mr. TUERK. I'm not looking for a particular conclusion, I am noting Dr. Schecter's relatively strong statement of an association between herbicides and cancer and Dr. Silbergeld's strong statement to that effect in her written testimony. Yet, as I look at the lung cancer section of the IOM report, looking at it obviously as a nonscientist, I find it very difficult to come to that conclusion myself when I see studies that are summarized by your group as being inconclusive. Some, like the farmer study and the 1991 Coggon and colleagues' study, would seem to indicate there is no association. And in only one or two of the studies—specifically Manz, which isn't explained very thoroughly in the IOM report, and Fingerhut, but only when we're talking about people with very prolonged and extensive exposures—do I find those data which would lead me to that conclusion. By contrast, the IOM report lists 10 or 12 other studies that would show either inconclusive results or negative results from the standpoint of drawing an association.

What I am getting at is this: As critical, unbiased scientists, Dr. Schecter, Dr. Silbergeld, perhaps others of you, how can you make such strong statements of association when, as I read Dr. Tollerud's assessment of the literature, I can't come to that same conclusion.

Dr. TOLLERUD. Well, speaking on behalf of the committee, because, as you are aware, the criteria for being on the committee is not being actively involved in dioxin research or herbicide research, I really can't go beyond what the report says. I think that your use of the word "inconclusive" needs to be carefully taken, in that the category that lung cancer was placed under was one of limited/suggestive. There was actually a substantial amount of spirited debate among committee members about what brief phrase to use for that category in order to convey what the committee meant. I think the statement reads reasonably well in that these are not disease categories to be dismissed and that the feeling of the committee was that they are also not in the same league as the cancers and other

conditions that were placed in the highest category of association. More research needs to be done. But there clearly is sufficient information in the literature to cause concern and I believe the committee felt that those were areas which should be focused on for future research by these scientists as well as others.

Dr. SILBERGELD. I would like to comment, because I think in part you have raised some very important issues and you've raised a number of them. To go back to one of them, I would like to reiterate that I don't think the answers are going to come solely out of studying the Agent Orange cohort, however we define it. As I mentioned before, I think one of the shortcomings of the IOM report was its failure to access and critically evaluate the entire relevant literature on the subject.

The basis for my comment that "scientists have generally concluded" is based on my own rather extensive involvement in dioxin research, as well as service on a number of other committees where that conclusion has been reached, including most recently the EPA expert panel reviewing the health risks of dioxin. I would be glad to go into that in considerable detail if you would like.

But let's talk about the two issues that you have mentioned to some extent. One is whether or not any of the information we have now allows us to go from what you have characterized as the relatively high dose intensive exposure situations of the NIOSH cohort down to considerably different situations which may relate to the Vietnam experience, and also whether shorter periods of exposure may or may not be able to be evaluated on the basis of studies that have dealt with longer periods of exposure. The second point you raise has to do with whether or not there is scientific basis for the issue of assigning some association worthy of compensation to lung cancer. I would like to treat those separately.

First, I think you do some misinterpretation, if I may suggest, to the import of the NIOSH studies. I would be happy to go into the publications of Fingerhut and her colleagues in as great a depth as you would like at this point or later in amplified submission to you. But the bottom line is that it is not in those studies—the IARC as well and the Yusho, the Yucheng, and the Seveso—it is not that cancer suddenly appears only at the high end of the scale. In fact, all the data that we have, whether we stratify the populations by the amount of time they were exposed, which goes to one of your questions, or by the imputed total dose, which goes to the other point—and they are very good questions—there is in fact a trend which goes over the entire temporality or cumulative dose scale. It is only at the ends of the scale that statistical significance can be discerned on a bivariate test of different incidence of cancer. But a trend analysis shows that the entire continuum of exposure is, in fact, increasing risk.

If one adds to that some of the other studies—the Mont study, Hardell studies, and others on cancer, as well as the farmer registries conducted by NCI over the past 6 years—one can, if one wishes, attempt to fill in the blanks from the very high dose studies down to the "background" levels in our own modern American population. I don't think that there is any evidence of a sudden break, but it is rather like smoking and other kinds of well-defined

carcinogenic exposures in that there is a very smooth dose-response curve.

But now let me suggest to you, and you may take this as the bias of an experimental scientist, that I think the real resolution of these issues comes from an understanding of the mechanisms of dioxin. Epidemiology at some point must be silent over the critical issues that you're pointing to, which is exactly what are the risks at low doses and is it reasonable on a policy basis, making real world decisions not ultimate scientific decisions, to infer that there would be some dose worthy of consideration by the U.S. Government at exposures in a range below the discernment of any epidemiologic study.

I would suggest to you that the molecular biology and mechanistic research which is comprehensively summarized in a volume of the EPA risk assessment process that Dr. George Lucier, Dr. Michael Gallo, and I were involved in preparing does, in fact, support the notion of a very smooth dose-response curve down to extremely low levels of exposure. I would be glad to submit any additional information you would like on that point.

Finally, let me deal briefly with your concern about the issue of lung cancer, and certainly that decision is not one that we were called upon to comment about in this testimony. But I would only note one very important issue about the dioxins which may—let me stress "may"—be relevant to lung cancer, but it certainly I think is probably why Dr. Tollerud's group was seriously impelled to think about these issues; and that is, both the epidemiologic and the mechanistic data that we have suggests very strong interactions between exposure to these types of chemicals and other experiences in the life of humans which predispose the risk of cancer and other health outcomes.

You should know that in a number of the cohorts that have been examined, there is evidence for what Dr. Schecter suggested, and that is an interactive effect between dioxin exposure and other chemicals. For example, in the nitro West Virginia work force, there is a very strong interaction between dioxin exposure and peritaminobiphenyl, a demonstrated human carcinogen, in perhaps multiplying but certainly greatly increasing the risks of bladder cancer. There are data suggesting an interaction between the effects of smoking and dioxin in the Seveso and other cohorts on cardiovascular disease and stroke.

So that it is the nature of these compounds—and I suppose if I were pressed to give one word to describe dioxin, I would say hormone—it is the nature of hormones and synthetic hormones to interact with other conditions naturally occurring and other burdens of a chemical world to increase risks. Let me stress again I don't think you are going to get the answers from simply studying the Agent Orange group alone.

Again, I regret the purview that the IOM imposed upon itself for reasons I don't understand in attempting to reach very difficult decisions with a self-defined body of evidence placed in front of it. I believe, as I think most scientists in the field believe, that it is only through a wise and judicious consultation of all the relevant information from molecular through human epidemiologic studies that

we can hope to serve you who are, after all, asking the relevant and real world questions that need to be answered.

Mr. TUERK. Dr. Stellman.

Dr. STELLMAN. With all due respect, your relevant and real world questions made me bristle because I think that part of the pressure that has been ever present in this whole issue of what we were asked to address here, which was followup research, has been the pressure—whether it be for Vietnam veteran compensation, for the implications of research for international liability, for the implications of this research on controlling the paper and pulp mill—I think it has been the burden on Vietnam veterans that they had the unfortunate circumstance to have been exposed to an industrial chemical of huge social significance. Had they been exposed to some chemical to which only they were exposed, we probably could have gotten on with this a long time ago.

So in a way, it is unfair for you to bring to us a question of a rather interesting decision that the VA made to compensate lung cancer when that is not what we were prepared to talk about here. Which raises a whole other set of questions, and that is what are the moral, ethical, and political bases appropriate for compensating people who were exposed. I am not prepared to have a discussion on whether or not I agree that the VA should or should not compensate its veterans for lung cancer at this particular point in time.

I am here to discuss, if we want an answer to what the health effects of exposure to herbicides and other occupational environmental hazards of Vietnam were, how shall we pursue that. Then if you want to have a separate set of discussions of how do we take the world of science and translate it into the very real world of helping people cope with their problems, to what extent do we compensate a worker exposed to a particular substance in the presence of lifestyle exposures. Those are all separate issues.

Again, with all due deference, I think this is exactly what we've been burdened with for all of these years. That is, lurking behind everybody's mind is, if we do this and this, what are the sociopolitical and economic implications.

Mr. TUERK. One good thing, Dr. Stellman, you don't have to be very deferential to staff people.

Dr. STELLMAN. OK. I am really angry that you asked that question. [Laughter.]

Mr. TUERK. From my standpoint—and Dr. Kahn, you're next—it is not often that we get a chance to have an array of physicians and Ph.D.s in front of us to discuss all these issues. I wish we had the chance more often. The last time we had such a panel before us, the IOM report had just been dropped in our laps and we weren't prepared to discuss it with the panel. So I do understand the unfairness of trying to explore some issues—although I was careful to ask no one to express an opinion on whether they thought VA had made a good decision or not.

Dr. STELLMAN. Well, I am happy to give you all kinds of opinions. The reason I bristled was that one of the last times I showed up here I was practically lassoed into testimony before a House committee for which I had been totally unprepared. I think we should put this question aside until you decide what you want to do as the Senate in answering the health questions. Then you have another

set of hearings on how long is this going to take, and what do we do in the interim, and what direction do we give, and how are we going to pass new laws to help the veterans get on with their lives.

Mr. TUERK. Before I kick it over to Dr. Kahn, I'll just state that Dr. Stellman's statement illustrates our problem. We have a hard time setting aside the science until we make decisions; we hope that science will help us make the decisions that have to be made. That is the frustration that we feel. We face a number of pressures as well, and we, as staff members, would like to recommend to our bosses, the decisionmakers, that they make decisions based on the best available science with all its limitations. That's why I want to explore the limitations of current science, and the extent to which we can rely on it to draw conclusions. And to the extent that exploring this issue here and now is unfair, I apologize. Maybe we can have another meeting informally with staff for that.

Dr. Kahn.

Dr. KAHN. I bristled, too. But I think it is an issue that ought to be explored here. You get into an unproductive circle of the following sort, which is exactly what you've raised, and it is a can of worms. I have had phone calls from news reporters who say, "Doc, what have you learned this week?" "Why does it take so long?" "The State of New Jersey spent all this money and it has been a year since you've said anything." Well, it takes so long because it takes so long.

Mr. TUERK. We get those kind of phone calls, too.

Dr. KAHN. Right. You've been on the other end of the phone, I guess, in similar circumstances. If you want to get it right, you are going to have to take your time and get it right. It can't be done the way you do McDonald's hamburgers. That is all there is to it. So you end up in an inevitable public policy box in which people who have to formulate policy and take immediate action for the benefit of humans who are alive and kicking today have to do so on the basis of imperfect information. There is no way out of the box.

What you can't do is hold a gun to our heads and say, "We've got to have the answer by July 1, 1994." We can't give you the answer by July 1, 1994. If you want to get an answer at all, it is going to require continued support over a long period of time and you people will extract from that as much information as you can as you go along.

I do want to suggest a way out of the box. First off, you can get an answer in time. You can get a series of small answers as you go along, along the lines of what Dr. Schecter and others on the panel here have mentioned, with a series of small focused projects that take less time to do. And each of them gives you something of value. Over time, you will learn something that will inform your policy decisions.

Now, there may be a way out of the intense pressure that you are under and that as a result we end up being under. There is an approach to the compensation issue—even though that is not on the calendar today, it has been raised and it might as well be dealt with—that I've thought about for some time and some of the other members of this panel have as well, particularly Dr. Albanese. I've thought for a long time it ought to be possible, in a strictly policy-

type decisionmaking process, to arrive at what you might loosely call the "dioxin syndrome," or an "herbicide syndrome," if you want to broaden it to other herbicides. It is a collection of medical and laboratory findings that you might see in persons who are affected. You would not expect to see all of it in any one person, but any veteran, male or female, who showed a significant collection of those findings—and you can argue as to what significant would be—would qualify for compensation based on the degree of disability.

Over time, that syndrome would have to be changed, refined. As new results come out, you would put more into it or you would take something out of it. But at least in establishing such a thing as a basis for compensation, you would then take the pressure off the science so that we could go our merry way and get you good answers as opposed to fast answers. That way we wouldn't be under the constraint of having to produce something next week or next month for show-and-tell. We could let it develop in an organic fashion, drawing on all possible sources of information that are out there in a process which is very complicated. That might be the way to get you people off the hook so that you can make intelligent compensation decisions and get us off the hook so that we can go about doing good science without feeling intense political pressure to come up with something right away.

With respect to the third point that you made, is there any way to take work that is done on persons of heavy exposure and extrapolate that to the Vietnam experience. I agree fully with Dr. Silbergeld—there isn't any threshold. The lower the dose, the smaller the fraction of people who will show a response, but you will never hit zero until you hit zero dose.

Mr. TUERK. I don't think Dr. Albanese has had a chance to respond.

Dr. ALBANESE. I would like to respond to your questions. I think there were three questions. No. 1 is, can we progress? Absolutely yes. And I think if you will provide a better workplace for the Government scientists, you will progress a lot faster. In fact, you may have been 10 years ahead of yourself had that been done before.

The second question. Can we extrapolate down? By all means. And as an older man who has been around a long time, I can assure you that anyone who wants to say something hasn't hurt you will bring up the idea that there is a threshold below which you are safe. It almost never is the case. The notion of a threshold, particularly if you look at the radiation sciences, is closely tied with the attempt to permit exposures, and they are almost never safe.

Dr. KAHN. And that's a political one, not a scientific one.

Dr. ALBANESE. Third, your idea about compensation. No. 1, I have studied the lung reports as well as I can and I think the evidence indicates that it is more likely than not that herbicide has caused lung cancer in veterans. So you have to do with that what you will. But I think there is a value that you're missing in your communication—one that I feel very, very deeply and I wish you would share with me—and that is, whenever any employer puts an employee in a situation where he is experiencing a novel environment, one that has not been studied before, that employee deserves

regard and perhaps even compensation which one might call "hazard duty pay."

The exposure to the Vietnam veteran was unprecedented in terms of his chemical environment. You have to bring an increased sensitivity to that fact. He may deserve compensation just because he was exposed to a novel environment that has not been appropriately studied. You must leaven all of your thinking with that; I would ask you to.

Dr. TOLLERUD. I would just like to briefly echo what I think has been said a couple of times here, and that is that the issue of compensation and how compensation is applied. The development of that policy, both a specific policy for veterans and Vietnam veterans, but in a more general sense how compensation is administered by a governmental organization, how that policy is developed, what are the inputs to it, what are the values that are balanced—I think that is a different scientific question. It is perhaps a political science question or a social science question, but I think it is not a question that should be taken lightly.

We were fortunate, if you will, in the Institute of Medicine in that policy implementation or development of policy was not the question that we were asked. But I think in our subsequent discussions of the committee after the report was issued, we in general agreed that it is an issue which merits debate. And I would like to echo what Dr. Stellman said and what Dr. Albanese said, which is that the fundamental question is not the degree to which lung cancer is linked to Agent Orange versus cigarette smoking versus an interaction of the two. If you are going to develop policy, you need rules by which you develop policy and by which you develop a compensation scheme.

I think that is the central debate. And that opens up a whole range of questions which are not molecular questions, they are not epidemiological questions, they are policy questions. I would suggest that there is benefit in studying that in and of itself and then bringing that information back to the specific issue that we're discussing here, which is Agent Orange.

Dr. STELLMAN. And if you're going to talk about lung cancer and smoking, I would like to draw your attention to the pretty sad facts that we found among Vietnam veterans who are members of The American Legion. I don't remember exactly the numbers, we can submit this to you, but the soldiers, the veterans who were in the heaviest combat and who had the highest exposures were smoking I believe four times as much, and I can't remember, but there is a huge gradient of smoking, divorce, alcohol. The people who suffered these exposures in many ways had their lives fall apart around them.

Mr. TUERK. Just to clarify. You are talking about smoking habits today or back then?

Dr. STELLMAN. Today. Smoking habits today. The war is a continuing burden to the Vietnam veterans who fought it. There is a very high correlation between the combat exposures and the herbicides exposures. So if you are going to ask these policy questions, there are many, many things, following up what Dr. Albanese was saying, that in fairness have to be tossed into the pot, separate

from the issues of how do you develop a good exposure measure for an epidemiology study.

Mr. TUERK. Actually, that's a fascinating point, especially in light of your prior comment about the potential relationship of stress and dioxin or herbicide exposure to negative outcomes; whereas it might be that stress would lead to other behaviors, such as smoking, which in conjunction with dioxin exposure might lead to negative results.

Dr. STELLMAN. There are two studies, ours and then the much larger one which in fact the Government paid for which was the Readjustment study, the results of which are virtually identical, illustrating the many ways in which the personal lives and habits of the veterans have been and continue to be disrupted in these ways.

Mr. TUERK. I've taken way more than my share of the time we have. So now I will only ask Dr. Schecter if you care to comment further. You opened up this dialog, and people have commented on what I said and what you said. If you would care to comment further, I would just like to invite you to. Otherwise, I will turn it back to other people to ask questions.

Dr. SCHECTER. Let me keep it very short. Again, I would reemphasize what other panelists have said, and that is that the IOM–NAS report did not consider most of the world's literature on dioxin-like chemicals. So there is a valuable body of data from elsewhere in the world that does have direct relevance.

Second, the policy issue I think which you opened up, a little to our surprise, on the lung cancer issue, I think Dr. Jeanne Stellman threw out a very interesting closing perspective from a policy point of view. If it was the stress of combat in a difficult war that led to increased smoking and increased cancer, then maybe lung cancer might be considered as compensable whether there was Agent Orange or dioxin exposure or not. The issue of other bad things that happened in Vietnam or in any stress or war of course needs to be considered. It is an interesting policy suggestion.

Mr. TUERK. It is that. I thank you all for making the point and reinforcing the point that needed reinforcing, to me at least, that there is a universe of literature out there that isn't summarized within the IOM report.

With that, I will kick it back to you, Laura, and ask my fellow minority staff members if they would care to ask questions.

Ms. PETROU. I just want to make two points. First, there are five additional NAS reports to be issued over the next 10 years. This is not the final word, and I'm sure Dr. Tollerud—I don't know if that is with joy or not—is well aware that five more are coming. [Laughter.]

But there is a lot more to be done here, and we're on the road.

The other thing is to get us out of this policy box because we didn't ask NAS to determine policy. Also, there is a law already in place to determine policy, to ensure that it is determined. So in some sense, I am sure we have many more policy fights to come, but we have a 15-year policy fight behind us as well. So that shouldn't be lost on anyone.

But just one question, and maybe it will help us with the lung cancer issue a little bit, and that whole issue of the category II dis-

eases. Dr. Tollerud, I would just like to ask you something I've probably asked you before, which is, is there any scientific basis on which you would draw distinctions between the multiple myeloma, prostate cancer, and respiratory cancers within category II with respect to the strength of the evidence?

Dr. TOLLERUD. In all of the committee deliberations, that point was explicitly discussed and there was not a consensus among the committee to distinguish between diseases within each category.

Ms. PETROU. Some might wonder what happened with prostate cancer, too. So it is a double-edged sword within that very category, and that is the policy decision that the VA made.

I have several more questions to ask, but if anybody else here has any, ask away. One question I have is about the Ranch Hand Study and the NAS recommendation that an independent, nongovernmental scientific panel be established "to review and approve a new expanded research protocol for both populations"—meaning the Ranch Hand and Army Chemical Corps populations—"and to commission and direct a common analysis of the results." There has been a lot of discussion about that recommendation and what it means. I know the VA has suggested that the Ranch Hand Advisory Committee be the advisory committee for both studies. My boss has a lot of concern about that, as do others.

I guess, Dr. Tollerud, I would like you to start off that discussion by just addressing what, in fact, the committee was recommending. My interpretation was not that the studies be done as they are being done and have someone else review them, but that we use the data and essentially start over in some aspects. I would like you to explain what the report actually recommended and then have any comments from the rest of the panel about how we ought to handle that data.

Dr. TOLLERUD. OK. First, the committee made no judgment or didn't evaluate any current standing committees per se as to whether they would fulfill the criteria of independence. I think the fundamental nature of that independence have been stated fairly clearly; that it should be nongovernmental, it should be filled by individuals with relevant expertise which is specific for the task of each of these committees, and that expertise would vary somewhat between committees, but in general each committee would have a fairly broad scientific expertise.

The expectation would be, from the IOM Committee standpoint, that the individuals on these committees would be free from bias, free from bringing to the table preconceived notions, and free from the influence of governmental associations. To that extent, I will simply make an observation about the Ranch Hand Advisory Committee. My understanding is that it is currently chaired by a Government employee and other Government employees participate as full members. As such, that would not meet the standard that the IOM Committee recommended.

Ms. PETROU. I should explain, too, that we have talked with the VA about this, and their reason for that recommendation was that they have been told that there is a moratorium on new advisory committees at this point. So there is a technical problem that we would have to get around.

Dr. Silbergeld, since you are on that advisory committee, you may have something to add. I know, Dr. Albanese, you may have some thoughts based on your experiences with the advisory committee and with the study in the past.

Dr. SILBERGELD. Well, with respect to the technical block on advisory committees, I believe some agencies have found some ways to get around that. Presumably there would be ways to handle that as well.

I think above and beyond the structural recommendations, the insights that you have heard from everyone, the fact that the current process just does not have the full faith and trust of practically anybody is sufficient reason to start again. Even if in an ideal world it could and should have worked, at this point in time it is widely perceived not to have worked. Merely to impose it again I think would jeopardize the investments that you might wish to recommend to continue to be made here.

Let me say just one thing though, and that is that in my experience, I don't believe in the concept of looking for unbiased people. I think it is sort of like picking juries—that if you look for people who don't have any biases on a situation, sometimes they turn out to be people who have no knowledge of the situation. My most useful experiences on EPA and NAS Committees have been when the biases have been fully acknowledged and an attempt has been made to both seek and obtain the most knowledgeable people and then to the extent necessary to balance the biases. I have found that those committees where the biases are made known—and all these committees begin usually with a very intense and revealing discussion of biases which helps introduce the committee members to each other, and then lays many cards on the table—this process does not then remove from the public service the opportunity to consult with and gain the knowledge that people who may be perceived rightly to be biased might bring to a situation.

I think this criterion that the Academy seems so enamored of is an erroneous way to approach getting the best information for Government. In the same way, I think there are Government scientists who could bring much to bear on this issue. So the knee jerk exclusion of Government experts from such a process I think is going to make your resources less valuable than they could be.

So, I would urge a very different approach to how one would get this advice. But certainly I would concur that, merely for reasons of history at the present time, you must start anew.

Dr. KAHN. Could I add something here. As a human being, as a man who puts his pants on one leg at a time in the morning just like everybody else does, you cannot help but have sympathy for veterans and other people, not veterans, who are in pain and who have some moral claim on us as citizens. Certainly that side of me and of everyone else here in this room is not to be denied. That being said, however, as a scientist, I try to look at data with a cold and beady eye. I am prepared to accept negative results if the results are well done, if the study is carefully crafted, if it is fairly presented, if the possible loopholes are discussed, which is the way I try to write my own papers.

I am not prepared to accept science that is shoddily done or where loopholes are obscured and stuff of that sort. So if a study

really does come out negative, fine, I'll live with that; if it comes out positive, I'll live with that too. I don't really care as long as good craftsmanship and honest presentation go into it.

I don't see why having the views of a citizen on one side should either qualify or disqualify someone from taking part in or serving on any sort of advisory group. That is about all I can say on the subject. Ellen is right. You cut yourselves off from people who have a great deal to contribute if you don't go out and seek a broad range of views.

Dr. TOLLERUD. Just perhaps a brief response from having lived through the process of being on the committee and coming into the committee without a decade of experience in the field. To perhaps play off the analogy, I think all of us at one time or another have expressed a problem with the jury system, but in decades, if not centuries, of experience, we have yet to come up with a better system.

The committee, in fact, did seek far and wide for scientific input, for public input, input from veterans, input from anybody who cared to come out and speak with us, including the members at the table here. It is not an easy process; it is very difficult. I think after the first meeting, many of us wondered what it was we had volunteered for. It is an immense task to try to reassess the incredible volume of scientific information available on a subject like this.

But I think you do bring a fresh perspective to the table. We have had lengthy discussions about whether it might not have been better to use the concept of balancing bias. I guess we didn't come to a vote on that, but my sense from the committee discussions was that the major unknown in balancing biases, the major difficulty, particularly with committees which stand for a long time period—I think that may be more tractable over a relatively short term—but over time, dominant personalities begin to play dominant roles. And to the extent that those dominant personalities come to the table with a bias, there is risk I think in those biases taking over over time.

I think that in addition to the fresh perspective that the committee members brought—members who were not simply chosen at random from the population, but each person brought to the table a specific scientific expertise relevant to the questions that were being asked—in addition to taking a fresh look at the scientific information, I think we found it easier, not easy but easier, at the end of this long process to come to a consensus with which we could all live. There was a lot of internal discussion but in my heart I believe that discussion, as long and difficult as it was, would not have come to closure in a timely fashion if we had come to the table with a decade of experience, if you will, or viewpoint that had been developed, because I think accepting a group a consensus would have been much more difficult.

So we found, even in retrospect, and perhaps it is not a fair statement to evaluate ourselves, but having gone through the process, the committee and the IOM staff I think came to the conclusion that it was in fact, for an area as contentious as this in particular, it was in fact a very useful way to construct a body to look at the information.

Dr. SCHECTER. I am also struck by the fact that many people were not heard, many facts were not considered. You did not invite anyone from Vietnam, the world's largest Agent Orange or dioxin incident, the place where it occurred. There are research scientists there. Dr. Bertazzi from Seveso was not asked to summarize the epidemiology. Dr. Shu from Taiwan was not invited, nor was Dr. Rogan, to the best of knowledge, to summarize the Yucheng rice oil poisoning. Dr. Masuta or Koretsuni were not invited to present the voluminous published data and what they have learned, including lung cancer findings, and preliminary epidemiology from the Japanese rice oil incident.

To me as a physician, what was done in a process, although I am very impressed with the individuals who served on the committee—it is as though we were going to discuss how to do a specific procedure in brain surgery and we decided we would exclude brain surgeons because they had biases on the subject. That means that many facts were not known or considered.

Dr. STELLMAN. When you were first working on putting forth this idea of having the Academy do the review, I was very worried about what would happen because I was worried that there would be the continuation of these huge political and very powerful political influences on the process. Then when the process was undertaken and began, my worry changed when I saw the constitution of the panel. I wasn't any longer worried about the political influence, I was just wondering how they were going to possibly get through all of this information in essence not knowing very much in specific about the field, and also because so much of the data was hidden, was not published, was not any place where they could do a medline search.

I came away I guess the same way I felt after I was sequestered on an attempted murder jury, that it was at one time one of the worst experiences of my life and also at the same time one of the best experiences of my life in seeing this process work. And, yes, there are lots of things that they left out, but I don't think they could have survived much more frankly. I mean, they weren't paid. It was just an enormous task. Somehow it worked to a very large extent.

So, I held my breath seeing what was going to come out, but I think they did the best that they could do. In hindsight, given the fact that they did do a good job, it was probably the right decision in keeping us biased people off because of how polluted this whole environment was. Now I am not sure in ongoing work whether that makes sense or not. I have to think about it. If you really want to get a nuts and bolts answer on where do you go from here, I am not sure it is the right way to continue. I think there is a whole universe of ways to proceed and we could all probably come up with different variations, but I think the variation that was chosen was a decent one with a decent result and that we should just go on from there.

Ms. PETROU. Dr. Albanese.

Dr. ALBANESE. I'd like to get back to your original question, and that is, if I understood it, whether the Ranch Hand advisory group should remain in existence. I would give you an unqualified "No." It is too dominated by Government individuals, but you need more

academic individuals, you need to retain some Government individuals, you need to bring clergy or laity representatives in, and you need to bring some veterans' representatives in to open the process.

I am very concerned about the Ranch Hand birth defects report. It is hard for me to accept that was approved by that peer review group. Frankly, just that fact alone would ask that we look again at that review group's process. I think the Ranch Hand birth defects report needs to be completely redone, the data need to be completely reanalyzed. The 1984 report on birth defects which was withheld by the prior peer review group needs to be published so that we understand the audit trail in that data set.

Ms. PETROU. Why don't you explain how long it was withheld.

Dr. ALBANESE. I don't think its been——

Ms. PETROU. Well, I mean, it was drafted in December of 1984, is that right?

Dr. ALBANESE. And it still has not been published.

Ms. PETROU. With an expectation that it would be published a year later. I thought that the final had been published.

Dr. ALBANESE. No, it has not been. And that report was not reviewed, for example, in the NAS report. It needs to be published to serve as a corrective to the 1992 report and to check the audit trail on how that birth cohort has evolved.

Ms. PETROU. We have someone in the back. Dr. Stoto wants to mention something.

Dr. STOTO. Since this is an informal hearing, I would be glad to have the opportunity to speak on behalf of the Institute of Medicine. First, I would like to say something in response to some of the comments that Dr. Schecter made and others have echoed. Dr. Silbergeld said that we had a self-imposed limitation on the body of evidence that we reviewed. Well, that's not true.

Dr. SILBERGELD. Then why did you exclude certain things?

Dr. STOTO. Well, we reviewed quite a bit of data. The book is thick, as you see, and we decided that we would cite the data that we thought were relevant. We are well aware of the Yucheng and the Yusho data that Dr. Schecter has mentioned over and over again. That, of course, was exposure to substances that were not in the herbicides that were used in Vietnam, although they are related chemically.

Dr. SCHECTER. No, that is incorrect. Dioxins were present, as reanalysis by Dr. John Ryan has shown, and the almost identical dibenzofurans are believed to have caused 75 percent of the pathology noted. And it is believed that dioxin-like PCBs caused probably the other 25 percent.

Dr. STOTO. The committee made the judgment that "dioxin-like" was not equal to dioxin. Now other people could have made a different judgment, and perhaps we should have included in the report our judgment about why we didn't think that was as relevant as some of the other information. But it is not true that we were not aware of those studies.

With regard to your comment about hearing from people and inviting them, everyone here at the table I think, with the exception of Dr. Kahn whose colleagues gave testimony in writing or orally before the Committee, was invited. In fact, we have quite a lot of information. We generally relied on the written record, the peer-re-

viewed literature and the other literature. That was quite abundant and we found that it was sufficient to make the judgments we were able to make.

With regard to the Ranch Hand reproductive study, in fact, there is quite a voluminous report of the reanalysis of that data. It has not appeared in the peer review literature but it has been published by the Air Force and that is reviewed in our committee's report. In fact, we have an appendix——

Dr. ALBANESE. There is a 1984 report, though, that was not made available to you because it has never been published as a Government report.

Dr. STOTO. But we have a copy of that.

Dr. ALBANESE. That is not reflected in your report.

Dr. STOTO. Well, we had a copy of that. We commented on the newer analysis of that although we made note I believe—we were aware of the findings of that one and we feel that our data fairly summarized what was there.

Dr. ALBANESE. I definitely think your data fairly summarized the situation in the reproductive report, but I think you are unaware of a report that was completed and never ever published.

Dr. STOTO. Admiral Zumwalt told us about that report, so we are aware of it. Perhaps there is other information that we don't know. We basically analyzed what we had and we know something about what was supposed in the earlier report. We didn't make comments on things that we didn't have access to.

Dr. ALBANESE. Understandably.

Dr. SCHECTER. I think your comment about those of us at this table having been invited except for Dr. Kahn—who was of course the key scientist for New Jersey and I am at a loss to understand why he was not invited to present all of the New Jersey data—but the Vietnamese who are doing active Agent Orange research were not invited because I was told there were insufficient funds to bring them. I think that is a serious limitation.

If you elect to not consider the Yusho and Yucheng, then you are denying the validity of the concept of dioxin toxic equivalents. There are hundreds of dioxins and hundreds of dibenzofurans and they do vary, but there is a concept that the U.S. Government uses which started in Binghamton, New York, that dioxins and dibenzofurans are qualitatively identical but quantitatively different. So I don't understand the scientific rational for excluding Yusho and Yucheng or Walter Rogan's PCB work on North Carolina mothers.

Dr. STOTO. All of the data from the New Jersey study were, in fact, reviewed by the committee. In fact, we reviewed some material that Bill Lewis gave to us in draft form.

Ms. PETROU. If I can interrupt, maybe what we will do is make sure that everyone is involved in the next round. I know that you will want to be, and I know that NAS did its best to include anyone who wanted to speak.

Dr. Kahn has something to say, and Bill had wanted to add something.

Mr. TUERK. I would only comment, since I thanked the panel members for pointing out that there was information that isn't fully reflected in here, I want to thank Dr. Tollerud and Dr. Stoto

for having explained what they considered, what they didn't consider, and why they didn't consider it, and not leave that point just hanging out there as it was. I appreciate your entering the discussion, Dr. Stoto.

Dr. STOTO. I think it is important to make it clear in the record that we did not exclude information from anyone in the world.

Dr. SILBERGELD. Could I ask one quick question about why the committee—and perhaps Dr. Tollerud can answer this—why the committee elected not to make even a reference to the experimental data base in helping perhaps reach some of the judgments that you came to.

Dr. STOTO. Did you read the hundred pages or so in chapter IV of the report?

Dr. SILBERGELD. I did. Yes. It is very out of date and it doesn't integrate it into the final decisions that are reached. It is as if it is a separate aside. It seemed to me that was some kind of strategic decision that was made which is certainly different from the decision made by other NAS and EPA Committees I've been on. So I just ask it as a question of inquiry.

Dr. TOLLERUD. First of all, I think there is some risk that we're going to degenerate into a discussion of the way the report and the way the committee was comprised. Just a brief comment that there was a feeling on the committee that the committee's task was, as defined by the law, to evaluate and discuss disease in humans.

We are all aware as scientists—and I am a biomarker person, one of the other hats that I wear—we're all aware of the whole issue of species variation. We felt that there was a large body of epidemiologic information that has already been referred to, which was sufficient to come to the conclusions that we were able to come to about human disease in humans, recognizing a vast additional amount of information generated in different in vitro systems, and in different animal systems which could be studied as well. But the judgment of the committee was explicit, it is explained in the early phases of the report, and that is the basis of the report. And the report can appropriately be criticized for those judgments.

Dr. SCHECTER. I would like to suggest to the Committee that many of the scientists from Asia, Drs. Koretsuni and Masuta from Japan, from Vietnam—where the average income is $30 a month for a physician—that the key scientists from any of these countries did not know of the existence of these hearings nor were they invited nor could they possibly afford to come unless sufficient funds are there for the next go round.

Ms. PETROU. Part of that may be my fault because I was one of the people who helped get mailing lists to IOM. What we can do, and I think should do, is get that kind of list of interested people to NAS so they can make them aware of things in the future.

Dr. KAHN. There are certainly things in the Academy report that if I had been doing it, would have been done a little differently. Anybody at this table will come up with something that we could have done a little differently. That doesn't mean that what you did was wrong. As I said in my testimony, I believe you took a very difficult issue and did a workmanlike job of it. I don't require that you touch all the bases and that everything be perfect. It was a decent, honest effort. You get another couple of shots over the next

several years to add more to it and, as things develop, I'm sure you will.

I don't want to see us fall into the trap of committee bashing. They made a good stab at it. While every one of us could have done something differently, I think that is not really what the issue is. The issue is what is going to happen next. And it isn't easy to formulate it. We've only barely begun to get at the question of who is going to do what the day after tomorrow.

Ms. PETROU. That's exactly my next question. David, do you or anyone else have anything?

Mr. BEST. Well, that goes to the question that I had. There are six specific recommendations listed in the executive summary and detailed throughout the report. I think I've come to the conclusion regarding the answer here to my question as to whether there is any consensus on the panel that these six recommendations are the way to proceed—and I fear the answer is probably no. We started on recommendation one and clearly don't have the time to detail all six.

Ms. PETROU. If you don't mind, maybe what we could do is weave in my question, which is very related, and let everyone answer a final question, and that is, exactly where do we go from here, who is going to do the research, what are the most important things for it to entail and are they the things in the six recommendations, and who is going to review this work? I know that is a huge question, and we don't have a lot of time. But if each person could quickly touch on the points that are most important in their minds with respect to that, that would be a good way to conclude.

Let me start with you, Dr. Schecter.

Dr. SCHECTER. OK. The report was good. We shouldn't have had to hold our breath. We hope the next one will be excellent or superior since we were generous in our suggestions.

The research chapter contains reasonable recommendations. There is basic science that needs to be done. We don't know how to extrapolate from fat or blood to the various organs of the body that we're concerned about, reproductive, cancer, and so on. We don't know how to do this yet. We don't know whether the dioxins in semen are the same as the dioxins in blood, same levels or pattern. We don't know whether in cancer the blood or fat dioxin levels for the various dioxins goes up or goes down. Very simple-minded questions.

Regarding the big question of exposure, I think we are in agreement that we need to try different methods. We don't want to have a method bashing. Each method has some validity. There are little studies in different populations, it has been repeatedly pointed out—Vietnam veterans, one population to study; occupational exposures also around the world; and Vietnamese in Vietnam. Men, women, and children should be looked at where they exist. There are populations where these exist. Small studies, frequently nongovernmental or working with actual research scientists in the Government where there can be collaboration.

Dr. ALBANESE. I congratulate the NAS on an excellent review. I agree with the recommendations. I would advise them to remain permeable to the outside world, including veterans and the laity.

I would make only one concluding remark, and that is I find that the VA's task force in their advice to the Secretary has been nonresponsive to the recommendations of the NAS. Those need to be carefully reviewed.

Ms. PETROU. Dr. Stellman.

Dr. STELLMAN. I echo that last sentiment about the VA task force. In my opinion, I think the VA should serve as a conduit for funds, if that's the way you have to do it, and that those people within the VA who can and want to do good research should be part of the same competitive process that is set up for doing research.

Among the six recommendations, it seems that four and five just naturally go together. That if you set up an exposure reconstruction, that you then have to evaluate it. So those seem to be actually one recommendation. I strongly disagree with recommendation two, having to do with the computerized index of their records. I think that should be scaled down to be a more pragmatic development of the system, which is I guess a modification of the recommendation—recommendation two with a practical viewpoint as to how to accomplish it. I think biomarkers are important, of course, for mechanistic understanding, but I think that we need to do epidemiology first and foremost, because it can be done, and the biomarkers should continue as the creativity allows. So I endorse No. 6 very much.

I think that perhaps the most useful way to proceed to actually make this thing operational is to look at the vast and very good mechanism that already exists within our own Government for doing research and funding research. I would strongly urge that the Senate turn to the National Institutes of Health, which has a well-developed mechanism for creating committees, creating external review committees, for writing research protocols and publicizing these protocols. The Division of Research Grants (DRG) is more than adequately set up for handling this situation. And there is no reason to exclude the Government researchers if they participate in the same DRG program that everybody else does. There are no wheels that need to be reinvented; they just need to be greased.

Ms. PETROU. Dr. Silbergeld.

Dr. SILBERGELD. I'm afraid I have to be a little less sanguine. I think that these recommendations are really still within a structure of the given—questions that are being asked as well as the structures that to date have been used with a little bit of amendment here and there. As I tried to say in my testimony, I find a great deal of concern, if you want to turn to page 12.6, that it seems that the focus of the recommendations of this committee is really, yet again, trying to understand the relationship between exposure to herbicides and cancers. And as I stressed, I think that the major issues that have always been issues for the veterans and are the major issues of the science as we understand the whole science—and I am still distressed by some of the answers I got from Dr. Stoto and Dr. Tollerud—are not so exclusively focused on cancer; No. 1.

No. 2, I think that we do need to examine whether investing all efforts on Ranch Hand is the way to get the answers we need. Let me point to another model that IOM has been very productive in

advising, and that is the DoD studies on breast cancer. For reasons best known to the Congress, a great deal of money was appropriated through the Department of Defense to study breast cancer. The IOM responded to a charge, I think excellently, in stepping outside the potential straightjackets that could be imposed both on what one might want to know and how one might find out what one wants to know. IOM has recommended I think an exemplary program of research and ways of obtaining, both over a very short and a longer term, the kinds of answers and resources that are needed to answer another very big question of concern to the American public.

But I would have to say that I do not agree with these research recommendations. I think they are based on rehashing a narrow issue of cancer and that the structure is a priori, defined within the existing research protocols, highly focused upon Ranch Hand and Vietnam veterans. There are other opportunities to answer the questions that I think Mr. Tuerk expressed very clearly. I agree very much with the questions that you asked, but I don't think that these recommendations are going to answer them.

Ms. PETROU. Dr. Kahn.

Dr. KAHN. A minor technical comment, and then I will address the specific question. To the extent that measurements of body burden will be undertaken in support of studies of veterans or anybody else, I think it is a grievous mistake to look only at TCDD. There has been a tendency for the Federal laboratory to do that. But I think that if you fail to look for the other dioxins, the dibenzofurans and now the PCBs, you miss a marvelous opportunity to flesh out what you can learn from the method. I won't go into further detail because this is not the place to do that, but I want to emphasize how stupid I think it would be if you are going to use this method at all to restrict it solely to determinations of 2,3,7,8–TCDD.

As to what do we do the day after tomorrow, I have watched what I call the top-down approach of the Federal effort develop over the years, where it is mandated from on high that a certain kind of study will be conducted. A few people put together a protocol and they may get some outside advice, but not a whole lot. But it is always top-down, and you sort of filter down to the level of the working stiffs who go out and actually do the research, they are working with a protocol that has been handed to them and in whose formulation they may not have had very much role. What you get from that are people who are working 9 to 5 jobs, who don't have a whole lot of personal investment in getting it right. You get a lot of confusion, a lot of turnover of staff, and you get bad work. That is one of the contributing factors to the failure of the Federal effort thus far.

The contrasting model, if you will, to the development of research is investigator-initiated projects which will have to compete by providing a proposal and passing peer review. You are right, we have the mechanism in place for doing that; it is called study sections. The NSF, the NIH, et cetera, all have them. An investigator-initiated project has one very, very powerful thing going for it, and that is the investigator thought up the idea and has a vested interest in making the project work.

I have learned from having done science with my own hands for a long time and from having taught innumerable students, that if you want to get the answer to a question, you have to want to know the answer so badly it hurts. It has to be a visceral desire to find out. It almost doesn't matter what you want to find out—if you haven't got that visceral desire, you won't find out anything.

And so I would ask, since the whole question is exceedingly complex, that strong emphasis be placed on having a large number of rather small investigator-initiated projects. There is one exception to this in the particular case of the Agent Orange problem, and that is the development of ways of accumulating a data base of military records, exposure information, the sorts of things that the Stellmans have done, that is something that probably can't be parcelled out in a series of small projects.

I don't have quite as clear a picture of how to do that as I do of the rest of the research. There, I think it is going to be necessary to give some person or some small number of people the go-ahead and the funds to pull together the means of developing what I would call the exposure data base that is going to be needed for a series of small projects initiated by other people. And the people who pull it together are going to have to be people who are highly knowledgeable in the area. I see no way that this is going to get done unless the Stellmans are involved. There are others of us out in the field who should have some involvement as well.

The evaluation of that by an independent group—I think that's worth doing and that would be a separate matter. And I think the Academy is on the right track here that the people who put it together should submit it for evaluation elsewhere and then, if necessary, go back and modify it to make it better.

That's about all I have to say on the subject. I want to emphasize for the record that unless people really want to know the answers, they aren't going to find them.

Ms. PETROU. Dr. Tollerud, we'll let you close this.

Dr. TOLLERUD. Thank you. First of all, I would like to say on a personal level that this kind of open exchange I think it very important, although I do also bristle. I think it is very healthy and kind of fun to see our collegial gloves come off at least for a little while and have a free and open debate. I would like to go on record, I guess, formally as vice chairman in saying that I agree with the recommendations of our own committee. [Laughter.]

I think it is really not a fair assessment to say that these are recommendations which are restricted or even particularly biased toward cancer. If you read through them, there is a clear intent to address things like reproductive disorders and other health effects which are clearly major issues and problems for veterans.

My second point is that I think it is also not fair to say that it is really focused on the Ranch Hands. That was one element and was intended to support a study which already has a tremendous investment that, with all of its limitations, has specific aspects which we continue to believe are very important, beginning with a reanalysis of data that is already in hand. It is quick, it is cheap, it is easy, and we think there is substantial information in hand which can be brought to bear on problems which continue to vex veterans.

And finally, to reiterate what has been said a couple of times perhaps from a slightly different perspective. I agree that TCDD and dioxin in its broadest sense was only one chemical or class of chemicals, and a contaminant at that, in Agent Orange. We were charged with looking at herbicides in a more broad sense. And for that I think epidemiology is the required approach. I think there is great value in studying individuals who were exposed to Agent Orange per se, be that veterans or Vietnamese or other individuals. Occupational studies and molecular studies can tell us a great deal about dioxin, but dioxin we believe was only part of the problem. Like the link between asbestos and mesothelioma, if we wait for understanding molecular mechanisms, we are going to miss whole large potential categories of human disease, for which we can define a link between exposure and disease without understanding the mechanisms.

We need to support the science. We need to develop biomarkers. I believe channeling money into the NIH process, into basic research to look at mechanisms, should go on as one component, but we should not neglect the epidemiology.

Ms. PETROU. Well, it is five after one. Unless somebody else here has anything——

Mr. TUERK. On behalf of Senator Murkowski and all the minority members of the Committee, I would like to thank you all for coming, for spending this length of time with us. We really appreciate that very much. This has been longer than the typical hearing. That is good news and bad news. I think principally good news.

Dr. KAHN. It's also been more fun. [Laughter.]

Mr. TUERK. I'll leave it at that. Thank you.

Mr. KIFER. On behalf of Senator Akaka and majority members, I would also like to express our appreciation for your being here. It is very gratifying to see the intensity and passion that can be applied to this. That I have not asked questions is not a lack of interest. What you have put forward, all of the give-and-take here, will be reviewed. You have raised many, many interesting questions. And as you do say, we have to look at policy issues here as well and how to apply them. And I certainly would not say that we would know how to do so, but there will be further research.

Having said that, I would just like again to express our appreciation for your being here.

Dr. SCHECTER. May I just make one comment. For those of you who are interested in the Agent Orange Conference in Hanoi November 15 through 18 of this year, I have a few handouts for you to take.

Ms. PETROU. David, did you have something?

Mr. BEST. I would just add my thanks and appreciation for your dedication to the cause of veterans. We value your experience and expertise on these issues.

I did have a question. I am not going to throw it out as a question but as a closing observation. Scientific inquiry generally, in my experience at least, leads to more questions than answers perhaps. The more we learn, the better we understand how little we know. I guess from translating your scientific inquiry, the 10 years in Vietnam, the 15 years preliminary, and however many years we are going to proceed, we, as a committee, and the scientific commu-

nity also, have to start thinking about where is the endpoint to this. I appreciate Dr. Kahn's remarks about not being boxed in, but it seems to me that at some point, without compromising the scientific value of this inquiry, we, as a committee, have to come to grips with some end point that we will translate into a public policy issue. So I thank the Committee and the witnesses.

Ms. PETROU. I just want to thank everyone. First, to NAS, in spite of any specific criticisms people may have, and I speak for my boss and I think for most of the Members of the Committee, you have done an amazing job for us. Some of the criticisms probably ought to be lodged at us because you did what we asked you to do, I thought maybe there are some exceptions that I could be convinced of. Maybe we didn't ask you all the right questions, and maybe that will have to be rectified. But I am pretty convinced that we couldn't be having this discussion today if it weren't for the work that was done in that report.

Having said that, I am also convinced that the report could not have been issued had it not been for the work of the other people here at the table. I am glad to see you all here and really appreciate your coming and your putting up with all the problems we've had in scheduling this hearing. Dr. Tollerud has been through two hearings that we've had problems with in the scheduling. So we really appreciate all the work that you've done and your being here.

Unless someone has something else, thank you.

[Whereupon, at 1:09 p.m., the meeting was adjourned.]

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Opening Statement of Senator Tom Daschle
Committee on Veterans' Affairs Hearing on Research on the Health Effects of
Agent Orange and Other Herbicides Used in Vietnam
November 2, 1993

On July 27, at a hearing before this Committee, the National Academy of Sciences released its first report pursuant to the Agent Orange Act of 1991 reviewing the scientific evidence related to the possible health effects of exposure to Agent Orange and other herbicides used in Vietnam. While much attention was given to the report's discussion of disease outcomes -- and rightfully so -- one of the most important aspects of that report received little public attention at the time it was released.

The research recommendations in the NAS report provide an important framework for today's discussion of where the search for the truth regarding Agent Orange has taken us, and where we need to go from here. Just as important will be the discussion of how we get there. The scientists who have quietly done some of the most promising work in this field -- sometimes in the face of overwhelming odds -- are here today to answer those questions.

Specifically, Congress and the scientific community need to focus on what research efforts offer the most realistic promise for finding reliable answers at a reasonable cost; how to develop accurate measures of exposure; and how to ensure that these scientific efforts are conducted and reviewed with absolute integrity. Once we define our research goals and methods, we will need to determine how the government's should facilitate their implementation.

There is a long history of government involvement in this issue, but it is not a very proud history. This Committee takes very seriously its responsibility to ensure that the government learns from its past mistakes and fulfills its commitment to the Vietnam veterans -- and their families -- who have suffered as a result of their exposure to Agent Orange. I am confident that today's discussion will lead us in that direction.

PRINTED ON RECYCLED PAPER

Testimony of
David Tollerud, M.D., M.P.H.
Vice-Chairman, Committee to Review the Health Effects in
Vietnam Veterans of Exposure to Herbicides
National Academy of Sciences
Institute of Medicine

Before the
Senate Committee on Veterans' Affairs
Hearing on Research on Health Effects of Agent Orange

November 2, 1993

Mr. Chairman and members of the Committee:

Good afternoon, I am Dr. David Tollerud, Director of Occupational and Environmental Medicine at the University of Pittsburgh Graduate School of Public Health, and the vice-chairman of the Institute of Medicine's Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. I am pleased to be here on behalf of the IOM committee to address issues related to research on the health effects of Agent Orange and other herbicides used in Vietnam, and in particular, to clarify issues raised in the IOM committee's report.

As you will recall, at your committee's hearing on July 27, 1993, Dr. Kenneth Shine, President of the Institute of Medicine and Dr. Harold Fallon, Chairman of the IOM committee provided your committee with a brief summary of the background on the committee's report and the Institute of Medicine as well as the committee's recommendations about exposure

reconstruction modeling and other research matters, so I will not repeat that information again. I am prepared, however, to answer any questions about these recommendations that the committee may have. For the record, I am including a full copy of Chapter 12 of the IOM committee's report as Attachment 1 to this statement[1]. This chapter lays out and justifies the IOM committee's research recommendations. I am also including a copy of Appendix C: Methodological Observations on the Ranch Hand Study as Attachment 2.

Today, I would like to address three specific issues: (1) the role of serum dioxin measurements in future research efforts, (2) the Ranch Hand study, and (3) the role of scientific advisory committees in further research on the effects of herbicides in Vietnam veterans.

Role of Serum Dioxin Measurements in Future Research Efforts

Since our report was released, we have become aware that some scientists have misinterpreted our conclusions as saying that serum dioxin measurements have no value in epidemiologic studies. Our report does not say this, and we would like to set the record straight that this is not the IOM committee's belief. The IOM committee does, however, feel that serum

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[1]Page references in this statement to the IOM committee's report are to the prepublication version released in July. Complete bibliographic information about the scientific literature cited in this statement can also be found in the IOM committee's report.

dioxin measurements are not a "gold standard" of exposure to herbicides in Vietnam, and they should not be relied upon as the sole measure of individual herbicide exposure in epidemiologic studies of Vietnam veterans.

Serum dioxin measures are discussed in a number of places in the IOM committee's report including: in generic terms as a biomarker (pages 6-9 through 6-11), as an exposure measure in Vietnam veterans (pages 6-26 through 6-30), with regard to exposure reconstruction (pages 6-35 through 6-36), and with regard to implications for further research in a number of places in chapter 12. Overall, the IOM committee's conclusions with regard to serum dioxin measurements were as follows:

> "New biochemical techniques that can detect small amounts of TCDD in the blood many years after exposure have some merit, especially for detecting group differences. However, because of common background exposure of all Americans to TCDD, poorly understood variations among individuals in TCDD metabolism, and relatively large measurement errors, individual TCDD serum levels are usually not meaningful. Furthermore, because not all herbicides used in Vietnam contained TCDD, serum TCDD levels are not good indicators of overall exposure to herbicides." [p. 1-3]

To explain this conclusion, I will address each of the scientific points underlying it. First, the IOM committee found that all Americans have some exposure to TCDD (dioxin). As detailed on page 6-9 of the report, "Normal exposure to TCDD leads to levels in the lipid stores of humans of about 5-6 ppt, as measured in the adipose tissue or the lipid portion of the blood (Needham et al., 1991)." However, "exposure to TCDD from environmental sources, primarily food (Geyer et al., 1986; Byard, 1987),

occurs on a continuing basis" in the general population. For instance "veterans with no unusual herbicide exposure had TCDD levels between 3 and 15 ppt (Gross et al., 1984)." The implication of these scientific results is that someone with an "elevated" dioxin level cannot be assumed to have been exposed to herbicides.

Second, not all herbicides used in Vietnam contained dioxin. As explained on p. 6-36 of the report, "some of the herbicides used in Vietnam such as Agent White did not contain TCDD, so it is possible for a veteran to have been exposed to a large amount of Agent White without having an elevated serum TCDD level at any time." This means that someone with a "normal" dioxin level cannot be assumed not to have been exposed to herbicides.

Third, there are relatively large laboratory measurement errors associated with serum dioxin measurements. As detailed on p. 6-10 of the IOM committee's report, a study of 337 Ranch Hand veterans indicated that the analytical measurement error (coefficient of variation) of serum dioxin measurements was about 22 percent (Pirkle et al., 1989). With a mean serum dioxin level of 5 ppt, a single individual's measurement could be off by more than 2 ppt in either direction. This does not imply poor laboratory practices, indeed the CDC dioxin laboratory is an excellent laboratory and their measurements are remarkably precise for this kind of work. It does mean, however, that quantitative serum dioxin measurements for individuals

are inherently imprecise, and that this variability needs to be explicitly taken into account in epidemiological studies.

Fourth, and perhaps most importantly, there are poorly understood variations among individuals in TCDD metabolism. Scientific data on these differences are explained in detail on pages 6-10 through 6-11 of the report as follows:

> "The pharmacokinetics of TCDD in humans--its distribution and passage through the body--are not fully understood, which makes individual serum TCDD levels difficult to interpret and also complicates the interpretation of epidemiologic studies relying on these measures of exposure. As described in Chapter 4, a complex, poorly understood process distributes dioxins among body tissues and slowly clears it from the body. There is evidence that this process is quite variable among humans, so it is difficult to model its behavior and thereby extrapolate backward to estimate the likely concentration of TCDD in fat or blood in the past. It is also assumed that TCDD is removed from the body according to first-order kinetics--that is, for a given period of time, a constant fraction of the TCDD body burden is eliminated--but some evidence suggests the process may be more complicated and may vary as conditions in the body change. Second, the metabolic processes governing this movement and disposition may not be relevant to the determination of the dose of TCDD to the brain or reproductive organs, for example. In the epidemiologist's view, there may be different "causal pathways" linking exposure to the biomarker and exposure to disease."
>
> "Variations in TCDD half-life estimates are likely to result from changes in weight and percentage of body fat. The normal aging process, as well as dietary changes, may play a role here. For example, an average 5 foot 10 inch male aged 20 to 24 years weighs approximately 70 kg, of which 15 to 18 percent is fat. If at age 40-49, this male weighs approximately 80 kg, fat content almost doubles. Thus, there may be an expected reduction in serum TCDD levels in Vietnam veterans just from the mechanisms of change in body composition with age (Albanese, 1991). If the percentage of body fat is found to significantly

affect half-life estimates, with assumptions of a 6- to 12-year half-life and increased body fat characteristic of aging, it is possible that a small or moderate intake of dioxin among Vietnam veterans may no longer be detectable by using current serum TCDD level as a biomarker (Schlatter, 1991)."

"Still other confounding factors may complicate exposure assessment. In a study of 640 Vietnam veterans, researchers found that serum TCDD levels varied with several personal characteristics, including age, race, body mass, and region of residence (Devine et al., 1990). It has also been suggested that disease may affect serum TCDD levels (Michalek and Tripathi, 1992). Flanders and colleagues (1992) have shown, for instance, that reverse causality, in which health outcomes affect the measured serum TCDD level years after exposure, can better explain some relationships between serum TCDD and health outcomes in the Ranch Hand study than a direct model in which TCDD causes the outcome."

Despite these difficulties, the IOM committee did find that

"serum TCDD measures are helpful in epidemiologic studies, but should not be taken as a "gold standard" of exposure. If there are group differences in serum TCDD levels, that probably does indicate a difference in exposure to TCDD between the two groups. However, even if there is a difference in TCDD exposure between two groups, it may disappear as subsequent serum levels fade to background levels with the passage of time between exposure and measurement. In particular, because of poorly understood variation among individuals in TCDD metabolism and relatively large measurement error, individual TCDD levels are usually not meaningful." [p. 6-11]

Group differences were felt to be more meaningful because in a group of individuals the factors leading to differences in serum dioxin measurements unrelated to past dioxin exposure would tend to average out. It is also important to note that because not all herbicides used in Vietnam contained TCDD, serum TCDD levels are not good indicators of overall exposure to herbicides. This is particularly relevant as the IOM committee found some

evidence to suggest that the herbicide 2-4-D rather than dioxin was responsible for the apparent association between at least one of the cancers studies and herbicide exposure.

The IOM committee went on to say that

> "Although quantitative measures of exposure are highly desirable, it may still be quite valid to use approximate measures of exposures or even surrogates such as the amount of time spent in a job in which the toxin was likely to have been used. Thus a biomarker, especially one gathered years after exposure, is not necessarily better than qualitative exposure measures based on process records. Group differences in serum TCDD levels can be useful in confirming that occupational exposure measures reflect true differences in exposure, as has been done in the NIOSH study (Fingerhut et al., 1989, 1991; Sweeney et al., 1990) and other studies (see below).

At the IOM committee's December 1992 workshop and in written material submitted to the committee in April, 1993, CDC researchers established their belief that laboratory measurements did account for all the variability in individual serum dioxin measurements. This finding is at odds with the scientific literature cited above. Furthermore, the IOM committee's review of the limited, unpublished data presented by CDC finds the results inconclusive. Further research may show that the CDC's view about the variability of serum dioxin is closer to the truth than the prevailing view in the scientific literature. In the absence of more concrete information, however, the IOM committee stands by the conclusions and recommendations in its report.

These findings suggest that while serum dioxin measurements are not a gold standard, they can contribute to epidemiologic studies if properly included in the statistical analysis. Serum dioxin measurements can also contribute to the evaluation of the proposed historical exposure reconstruction model. The IOM committee believes, however, that serum dioxin measures need not and should not be the sole source of information on exposure to herbicides in epidemiologic studies of Vietnam veterans, and studies should not be designed around serum measurements.

The IOM committee called for serum dioxin measurements to be taken for the Army Chemical Corps if they are to be studied in parallel to the Ranch Hand cohort [page 12-2]. The IOM committee also made a specific recommendation that "Biomarkers for herbicide exposure should be developed further." [Rec. #3, p. 12-4] The committee would not have made these recommendations if it believed that serum dioxin measurements have no value in epidemiologic studies. In explanation of Recommendation #3 , the IOM committee noted that

> "Considerable uncertainty remains about the use of current or future serum TCDD levels as indicators of past exposure to TCDD in Vietnam veterans. Further research on the toxicokinetics of TCDD is needed to permit more accurate extrapolation from current serum TCDD measurements to past exposures. The multiple serum measurements from the Ranch Hand study group and other highly exposed groups should be particularly useful in this research." [p. 12-4]

The IOM committee went on to say, however, that

"An individual's serum TCDD level, ... is at best an indicator of past exposure to TCDD; it does not necessarily reflect general exposure to all herbicides used in Vietnam. Further refinement of currently available TCDD biomarkers and improved understanding of TCDD metabolism so that these measures can be appropriately included in statistical analyses, as well as development of new biomarkers for exposure to herbicides per se, would also be useful." [p. 12-4]

Some of the research efforts mandated in P.L. 102-4 involved serum dioxin measurements, so the IOM committee addressed them as well (the rationale for these recommendations is described in detail on pp. 12-7 through 12-9).

"Section 6 of Public Law 102-4 requires the DVA to "compile and analyze, on a continuing basis, all clinical data" that (1) are obtained in connection with DVA examinations and treatment of Vietnam veterans, and (2) are likely to be scientifically useful in determining the association between disabilities experienced by these veterans and exposure to dioxin or herbicides. Such a system, called the Agent Orange Registry (see Chapter 2), currently exists. Section 7 of the law calls for the establishment of a system for the collection and storage of voluntarily contributed samples of blood and tissue of veterans who served in Vietnam. Balancing the strengths and weaknesses of stored biological samples and clinical data for research purposes, the committee feels that systems of this sort have scientific value, but only to the extent that they are components of specific, well-designed studies; see, for instance, National Research Council (1991). In the absence of a clear study design to guide such activities, and without resolution of important design, quality control, and ethical issues regarding tissue banks, the committee does not recommend the establishment at this time of the clinical data and tissue archiving systems described in sections 6 and 7 of the law.

The final mandate in Public Law 102-4 on which the committee must comment calls for the testing of serum of Vietnam veterans who apply for medical care or file a disability compensation claim for TCDD (section 9). The purpose of this mandate is not stated in the legislation. If research purposes are contemplated,

the committee's discussion about tissue archiving systems applies, and such a program would not be recommended at this time. It is also possible that this program is intended to provide information on individual exposure to dioxins or herbicides to aid in individual compensation decisions. The committee cannot make recommendations for DVA policy, but notes that the finding in Chapter 6 that individual TCDD serum levels in Vietnam veterans are usually not meaningful (because of common background exposures to TCDD, poorly understood variations among individuals in TCDD metabolism, relatively large measurement errors, and exposure to herbicides that did not contain TCDD) might apply to this mandate.

The Ranch Hand Study

As the IOM committee noted in Appendix C, because the veterans of Operation Ranch Hand are among those with the highest exposure to herbicides in Vietnam, because that exposure is well documented by records and serum dioxin measurements, and because the group has been the focus of extensive epidemiological and clinical observation, the Ranch Hand study represents one of the best available opportunities for understanding the health effects of exposure to herbicides in Vietnam veterans. The IOM committee thus reviewed all of the research reports concerning the Air Force's Ranch Hand study in great detail.

The IOM committee concluded that "Much can be learned by reanalysis of existing data or more in-depth analysis of data expected from current research programs investigating the health of Vietnam veterans, including

the Air Force Ranch Hand study and DVA studies of other highly exposed Vietnam veterans such as members of the Chemical Corps." [p. 12-2]

Consistent with this finding, the IOM committee has made the following recommendation:

> "The committee endorses continued follow-up of the Air Force Ranch Hand cohort and its comparison group, and recommends that members of the Army Chemical Corps and an appropriate comparison group be followed in a similar study. An independent, nongovernmental scientific panel should be established to review and approve a new, expanded research protocol for both study populations, and to commission and direct a common analysis of the results." [Rec. #1, p. 12-2]

As noted in the IOM committee's report, the Ranch Hand cohort includes the Vietnam veterans with the highest documented exposure to herbicides, and the committee endorses continuation of the planned follow-up, including both mortality and morbidity studies. A major limitation of the Ranch Hand study, however, is the small size of the cohort--1,261 men at the start of the study, 995 who completed the 1987 physical exam (Michalek et al., 1990) -- so studies of other groups, in addition to the Ranch Hand, that may also have been highly exposed to herbicides in Vietnam would be valuable. One such group is the Army Chemical Corps. According to a recent abstract, Kang and Dalager (1993) have now identified 2,954 Army veterans who held chemical operation positions in Vietnam. The IOM committee felt that continued follow-up of the members of this group would substantially increase the size of the highly exposed population of Vietnam

veterans and would yield greater statistical power to detect less common health outcomes. [p. 12-2]

The IOM committee has also recommended that priority be given to additional research on reproductive outcomes that would help clarify the possible effects of herbicides. On page 12-6 of the report, the IOM committee argues that

> "Since Vietnam veterans are expected to have relatively few additional children because of their age, reanalyses of existing reproductive data, especially those based on registries, with the new exposure reconstruction measures proposed in this chapter, would be especially relevant. In particular, the committee believes that extensive reanalysis of the Ranch Hand reproductive data could shed additional light on these questions (see Chapter 9 and Appendix C)."

In the course of its review, however, the IOM committee identified a number of methodological problems with the analysis and presentation of the data collected in the Ranch Hand Reproductive Effects Study (AFHS, 1992). The committee is aware of the logistical difficulties involved in such a large and detailed data collection effort, and it applauds the efforts of the Air Force research team in that regard. In addition, the committee also acknowledges the efforts of the Ranch Hands themselves to participate in the follow-up study; they deserve a great deal of appreciation for their efforts. Ranch Hand analysts seem to have made a good faith effort to be thorough in their analyses and to address a number of potential criticisms in advance, but the report is difficult to read and interpret for a number of reasons. The

specific problems with the report are detailed in Appendix C of the IOM committee's report, included as Attachment 2 to this testimony.

The Air Force has prepared a "Background Paper" (dated September 13, 1993) in response to the IOM committee's appendix and other discussion of the Ranch Hand study. Members of the IOM committee and I were grateful to receive this background paper, and we have read and considered it carefully and will certainly take it into account in any future reviews of the Ranch Hand results The Air Force background paper fairly characterizes our comments in two categories.

First, we noted that many aspects of the Ranch Hand report were difficult to understand. With regard to these issues, the IOM committee is pleased to learn that some of the analyses and tables that it could not find are indeed in the report. We appreciate their explanation; however, after reviewing these tables, the committee does not feel that inclusion of the tables alters the committee's criticism of the report.

Second, most of our comments in Appendix C relate to differences of scientific judgment regarding statistical methodology. With regard to all of these issues, the IOM committee recognizes that there are often legitimate differences among scientists about how best to analyze data, and we are pleased that a public discussion about the best ways to analyze the existing data has begun. However, having considered the specific rationale offered by the Air Force in its "Background Paper" for the choices its analysts made,

the IOM committee stands by its original critique and recommendations. In particular, we feel that several of the points we made (exclusion of low exposure levels from some analyses, too much emphasis on p-values, use of complicated interaction models that could obscure main effects if present) are critical ones that should be addressed in future analyses. Other issues (pair matching and within subject correlation) should, at the very least, have been acknowledged and discussed in the Ranch Hand report.

The IOM committee recognizes the possibility that extensive reanalysis of the data may not uncover any consistent positive findings. However, given the lingering questions in the minds of many about the association between reproductive effects and herbicide exposure, we feel that priority should be given to a reanalysis of the important Ranch Hand data by other scientists.

The Role of Scientific Advisory Committees

The IOM committee made recommendations regarding an independent, nongovernmental scientific advisory panel for the proposed Ranch Hand and Army Chemical Corps studies [Rec. #1, p. 12-2]. The IOM committee made a separate recommendation that a nongovernmental organization be commissioned to develop and test models of herbicide exposure for use in studies of Vietnam veterans and a second scientific advisory panel to evaluate the proposed historical exposure reconstruction

models. Although these three groups would serve different purposes, the IOM committee believes that independence from government is paramount to assure the scientific credibility of these groups.

The conclusion of a committee of the National Academy of Sciences convened to review the proposed protocol for the Ranch Hand study (NRC, 1980) is as relevant today as it was more than a decade ago: public perception of the federal government's interest in the outcome of the scientific studies related to herbicide exposure suggests that all such studies be conducted by nongovernmental organizations. Independence from governmental influence is needed in order to satisfy the public's concern about impartiality and scientific credibility. The membership of these scientific advisory committees is also critical; they must have the appropriate disciplinary expertise, as well as an independence of mind. Both of the advisory committees that we recommended require expertise in biostatistics and epidemiology as well as exposure assessment. The advisory committee called for in Recommendation 6 will need special expertise in historical exposure reconstruction in occupational settings.

This concludes my prepared remarks. I would be happy to answer any questions the committee might have.

ATTACHMENT 1

Chapter 12
Research Recommendations

INTRODUCTION

The committee's review of the existing literature has identified some health outcomes having likely or possible associations with herbicide and/or TCDD exposure and other outcomes for which the data are simply insufficient (Chapters 8 through 11). Even where an association with herbicide exposure is likely, the magnitude of the risk remains uncertain, especially for Vietnam veterans. Given this scientific uncertainty, the second part of the committee's charge—to assess the need for continued research efforts—is timely and appropriate.

As stated in Public Law 102-4, the committee must consider the available scientific evidence, the value and relevance of scientific information that could result from additional studies, and the cost and feasibility of carrying out such studies. Consistent with this mandate, two considerations have guided the committee's research recommendations. First, as discussed in Chapter 6, the interpretation of existing epidemiologic studies is compromised by the frequent lack of appropriate individual measures of exposure to herbicides or TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin). This is especially true for studies of Vietnam veterans, yet the committee believes that there may be substantial numbers of veterans who have been exposed to levels of herbicides equivalent to workers in the occupational studies that the committee reviewed. However, as outlined in Chapter 6, the committee believes that it is possible to develop better exposure measures for Vietnam veterans, for use in any future research efforts. Second, as chapters 8 through 11 have shown, substantial scientific uncertainty about the health effects of herbicides and TCDD remain, especially with regard to Vietnam veterans, despite the number of existing studies. Thus, the committee concluded that a series of epidemiologic studies of Vietnam veterans could yield valuable information if a new, valid exposure reconstruction model could be developed.

The committee's research recommendations focus on studies in Vietnam veterans rather than on general toxicologic research or on epidemiologic studies of occupationally or environmentally exposed populations. The substantial amount of research on the toxicology and epidemiology of herbicides and herbicide components already under way in the United States and abroad, although not targeted specifically to Vietnam veterans, is likely to contribute to the knowledge of potential health effects in veterans.

ANALYSES OF EXISTING DATA AND RESEARCH PROGRAMS

Much can be learned by reanalysis of existing data and by more in-depth analysis of data from ongoing research programs that investigate the health of Vietnam veterans. Studies of particular interest include the Air Force Ranch Hand study and the Department of Veterans Affairs (DVA; formerly the Veterans Administration) studies of other highly exposed Vietnam veterans such as members of the Army Chemical Corps.

Studies of Highly Exposed Vietnam Veterans

Recommendation 1. The committee endorses continued follow-up of the Air Force Ranch Hand cohort and its comparison group, and recommends that members of the Army Chemical Corps and an appropriate comparison group be followed in a similar study. An independent, nongovernmental scientific panel should be established to review and approve a new, expanded research protocol for both study populations, and to commission and direct a common analysis of the results.

The Ranch Hand cohort includes the Vietnam veterans with the highest documented exposure to herbicides, and the committee endorses continuation of the planned follow-up, including both mortality and morbidity studies. Because they will be available at three points in time, the serum TCDD measurements from this study are particularly important to better understand TCDD metabolism and to assess its use as a biomarker to further analyze health effects. Studies of individual characteristics and other factors affecting TCDD metabolism are particularly important and should be encouraged. This knowledge will lead to more appropriate analyses of the Ranch Hand data and other studies that use serum TCDD gathered years after exposure as a biomarker.

A major limitation of the Ranch Hand study, however, is the small size of the cohort--1,261 men at the start of the study, 995 who completed the 1987 physical exam (Michalek et al., 1990). Studies of other groups, in addition to the Ranch Hand, that may also have been highly exposed to herbicides in Vietnam would be valuable. One such group is the Army Chemical Corps, which has been studied by the DVA (Thomas and Kang, 1990).

Members of the Army Chemical Corps were responsible for the storage, preparation, and handling of herbicides and other chemicals. Although they were exposed to a wider range of chemicals, the level and intensity of herbicide exposure may have been similar to those of the Ranch Hand cohort. In their first study, Thomas and Kang (1990) identified 894 members of this group and obtained vital status for 745. According to a recent abstract, Kang and Dalager (1993) have now identified 2,954 Army veterans who held chemical operation positions in Vietnam. Continued follow-up of the members of this group would substantially increase the size of the highly exposed population of Vietnam veterans and would yield greater statistical power to detect less common health outcomes. Prompt collection and storage of biological samples and determination of serum TCDD levels for these additional highly exposed veterans would enhance future epidemiologic studies of health outcomes.

Further study of both groups is likely to yield information on a number of health outcomes for which additional research is needed. Priorities for specific health outcomes are discussed after recommendation 6. However, to be useful for this purpose, a common protocol must be followed for both groups. Thus, it is important that a new and expanded protocol for both study populations be developed to include sufficient data for assessing health outcomes.

The high participation rate of veterans in the Ranch Hand study (84 percent) is a credit to both the Air Force and the Ranch Hands themselves. However, the study could benefit from improved methods of analysis and presentation of results both for existing data and for data obtained in the future. Difficulties with interpreting these analyses, as exemplified in the recent reproductive effects report from the Ranch Hand study (AFHS, 1992), along with specific suggestions for further analyses, appear in Appendix C.

As a committee of the National Academy of Sciences noted in a review of the proposed protocol for the Ranch Hand study (NRC, 1980), public perception of the federal government's interest in the outcome of the study results suggests the need for studies of the health of Vietnam veterans to be conducted by a nongovernmental organization. Ranch Hand's excellent participation rate argues that components of the Department of Defense (DOD) or the DVA continue to conduct the follow-up examinations of the Ranch Hand and Army Chemical Corps cohorts. However, an independent, nongovernmental scientific panel is needed to oversee the analyses of the resulting data in order to satisfy the public's concern about impartiality and scientific credibility. Such a panel could commission others to perform the analyses or arrange to conduct the analyses itself. The panel should also ensure that data from the study are made available to others for secondary analyses within a reasonable time frame and with appropriate safeguards for individual confidentiality.

FEASIBILITY OF NEW EPIDEMIOLOGIC STUDIES OF VIETNAM VETERANS

As discussed in Chapter 6, one of the major problems with the interpretation of existing studies is the frequent lack of appropriate measures of exposure to herbicides or TCDD; however, the committee finds that it may be possible to develop better exposure measures for Vietnam veterans. In particular, Chapter 6 proposes measures that are not dependent on serum TCDD levels (which the committee finds inappropriate for the full range of herbicide exposures) but instead recommends the use of less formal sources of historical information about base perimeter spraying and other relevant exposures, as discussed below in Recommendation 4. Thus, the committee concludes that certain further research efforts using new measures of exposure to herbicides in Vietnam are both necessary and potentially feasible. However, each of the possible measures that the committee has considered involves some degree of nondifferential misclassification bias, and the effect of this bias on risk estimates would likely be to underestimate true effects if they existed, possibly to the point that they would not be detected. In particular, the committee recommends that the following steps be taken prior to undertaking new epidemiologic studies of Vietnam veterans, for the reasons described below.

Recommendation 2. The Department of Defense and the Department of Veterans Affairs should identify Vietnam service in the computerized index of their records.

Chapter 3 notes that Vietnam service is not a "flagged item" on the computerized index of military personnel records archived at the National Personnel Records Center in St. Louis, Missouri, which is maintained by the General Services Administration under an agreement with the Department of Defense. Therefore, the computerized index of the record system does not allow for searches or selection of records of individuals who have served in Vietnam. The lack of an indicator of Vietnam service complicates every epidemiologic study based on military records and leads to methodologic inconsistencies among studies in defining the population under consideration. Adding this indicator to the computerized data base would facilitate future mortality studies based on computerized records, thereby increasing accuracy and decreasing cost, and would also simplify other epidemiologic studies of health outcomes in Vietnam veterans. All servicemen and women who were stationed in Vietnam or in the Vietnam theater during the Vietnam era should be identified in the records.

Recommendation 3. Biomarkers for herbicide exposure should be developed further.

Considerable uncertainty remains about the use of current or future serum TCDD levels as indicators of past exposure to TCDD in Vietnam veterans. Further research on the toxicokinetics of TCDD is needed to permit more accurate extrapolation from current serum TCDD measurements to past exposures. The multiple serum measurements from the Ranch Hand study group and other highly exposed groups should be particularly useful in this research.

An individual's serum TCDD level, however, is at best an indicator of past exposure to TCDD; it does not necessarily reflect general exposure to all herbicides used in Vietnam. Further refinement of currently available TCDD biomarkers and improved understanding of TCDD metabolism so that these measures can be appropriately included in statistical analyses, as well as development of new biomarkers for exposure to herbicides per se, would also be useful.

Recommendation 4. A nongovernmental organization with appropriate experience in historical exposure reconstruction should be commissioned to develop and test models of herbicide exposure for use in studies of Vietnam veterans.

Exposure assessment has been a weak aspect of most epidemiologic studies of Vietnam veterans. The military reports and personal testimony reviewed by the committee suggest that a sufficient range of exposure to herbicides may exist among Vietnam veterans for valid epidemiologic studies of certain health outcomes, and the committee believes that it is possible to develop valid exposure reconstruction models for epidemiologic studies using methods of historical exposure reconstruction. Such models would estimate the likelihood that each

individual veteran was exposed to herbicides in Vietnam and possibly quantify their degree of exposure. These models (described in more detail in Chapter 6) would incorporate information from existing military records about troop movements and herbicide spraying (including, but not limited to, the HERBS and Services HERBS tapes). The models must also include less formal sources of historical information about ground and perimeter spraying, such as records of herbicide shipments to individual bases from the major shipping depots, and consideration of the types of terrain, typical foliage, and military mission of the bases or troops located there. Supplemental information gathered from surveys of military officers with first-hand knowledge of herbicide operations in Vietnam, such as the 1971 survey conducted by the Army (U.S. Army, 1972) could also be incorporated into the exposure model.

Historical exposure reconstruction is a well-developed specialty in occupational health research that requires substantial professional judgment. The committee recommends that the DVA arrange for a nongovernmental organization with appropriate experience in historical exposure reconstruction to develop and test potential models of herbicide exposure for use in studies of Vietnam veterans. This group will need access to DOD and DVA records to carry out this work.

Recommendation 5. The exposure reconstruction models developed according to Recommendation 4 should be evaluated by an independent, nongovernmental scientific panel established for this purpose.

Herbicide exposure reconstruction models for Vietnam veterans must be evaluated thoroughly before epidemiologic studies based on these models proceed. The committee has identified three possible approaches to such an evaluation, which are discussed in more detail in Chapter 6: (1) internal consistency checks, (2) comparisons of model exposure measures with serum TCDD measurements, and (3) assessment of the association between exposure reconstruction measures and health outcomes shown in occupational or environmental studies to be associated with herbicides. Scientific judgment is required in interpreting the results of such an evaluation, so the committee cannot specify explicit criteria for acceptance or rejection of the new exposure reconstruction models in advance of their development and testing.

The committee recommends that an independent, nongovernmental scientific panel be established to review the results of the proposed evaluation studies and judge the validity and feasibility of the exposure reconstruction models. This panel should have expertise in historical exposure reconstruction and epidemiology. To maintain the public and scientific credibility of the study, the panel members should be nongovernmental and independent of the organization that develops the exposure reconstruction models.

Recommendation 6. If the scientific committee proposed in Recommendation 5 determines that a valid exposure reconstruction model is feasible, the Department of Veterans Affairs and other government agencies should facilitate additional epidemiologic studies of veterans.

A number of possible epidemiologic studies could provide additional information on the health effects of exposure to herbicides in Vietnam beyond what is already known. Highest research priority should be given to those health effects for which additional study is likely to change the balance of the evidence for or against an association. This includes

a. health outcomes for which current evidence is limited/suggestive of an association (lung and respiratory cancers, prostate cancer, and multiple myeloma);

b. health outcomes for which current evidence is insufficient or inadequate to determine whether an association exists, but which, in the committee's judgment, are plausible based on animal toxicologic data (such as nasal/nasopharyngeal cancer) or for which there are known associations with related chemical compounds in humans (such as liver cancer and polychlorinated biphenyls; Nicholson, 1987);

c. health outcomes for which the typical age at onset has not yet been reached by members of the Vietnam veteran cohort (such as prostate cancer).

The committee also recommends that priority be given to additional research on reproductive outcomes that would help clarify the possible effects of herbicides. Since Vietnam veterans are expected to have relatively few additional children because of their age, reanalyses of existing reproductive data, especially those based on registries, with the new exposure reconstruction measures proposed in this chapter, would be especially relevant. In particular, the committee believes that extensive reanalysis of the Ranch Hand reproductive data could shed additional light on these questions (see Chapter 9 and Appendix C).

Although there is sufficient evidence of an association between occupational or environmental exposure to herbicides and non-Hodgkin's lymphoma, Hodgkin's disease, and soft tissue sarcomas, the existing information on dose-response relationships is incomplete, especially with regard to Vietnam veterans. If a valid exposure reconstruction method can be developed, it might be applied to the exposure data available from existing case-control studies to provide additional dose-response evaluations. Further refinement of the clinical and pathological definitions of soft tissue sarcomas in epidemiologic studies would also help to determine which of the specific cancers in this class are associated with herbicides and/or TCDD.

The exposure reconstruction models to be developed could be used in either case-control or cohort studies. The type of study design will depend on the health outcome being investigated. Rare health effects, for instance, will likely require case-control studies, as described in Chapter 5.

The cost of these epidemiologic studies will depend on the study design. A design based on an exposure reconstruction model applied to computerized troop location records using existing mortality data or health outcome data could be relatively inexpensive. Adding detailed record review by experts or analysis of clinical or morbidity data would substantially increase costs. A study design involving serum TCDD measurements would also increase cost, if current costs for the biochemical assays are not reduced.

Although the number of women Vietnam veterans may be too small to provide adequate statistical power in a study by themselves, the committee believes that women Vietnam veterans should be included in Vietnam veteran studies whenever appropriate.

The committee recognizes that the recommendations for development of a historical exposure reconstruction model and its use in epidemiologic studies might seem at variance with the Centers for Disease Control (CDC) (Pirkle, 1993), White House Agent Orange Working Group (AOWG) (Young et al., 1986), and Office of Technology Assessment (OTA) (Gibbons, 1987) conclusions with regard to the congressionally mandated Agent Orange Study. The committee has come to a different conclusion for four reasons: First, the CDC-AOWG-OTA conclusions were based in large part on serum TCDD measurements, which the committee feels are insufficient for validating exposure to herbicides used in Vietnam, as explained in Chapter 6. Second, the arguments underlying the earlier conclusion that individuals in combat units were widely dispersed and that troop movement data are incomplete imply that exposure measurements may be imprecise, not that they are invalid. However, these arguments do suggest that historical reconstruction of exposure will have some degree of nondifferential misclassification bias, and the effect of this bias on risk estimates would likely be to underestimate true effects if they existed, possibly to the point that they would not be detected. Third, the committee is proposing the use of more, but less formal, information on exposure than was considered in 1986. This includes the development and use of informal information on perimeter spraying, which might account for more meaningful herbicide exposure than the aerial spraying documented on the HERBS tapes. Finally, the committee does not know whether the approach it proposes will prove valid or whether new methods will identify a sufficient number of highly exposed Vietnam veterans for an epidemiologic study. In the committee's judgment, however, the likelihood that this approach will be successful is sufficient for it to be recommended.

MANDATED RESEARCH EFFORTS

For the purposes of further research on the health effects of Vietnam service, Public Law 102-4 mandates that the DVA establish four specific programs: (1) a scientific research feasibility studies program; (2) a system to compile and analyze clinical data obtained in connection with the examination and treatment of certain Vietnam veterans; (3) a tissue archiving system; and (4) a program of blood testing for certain Vietnam era veterans. These programs are subject to initiation, continuance, or discontinuation depending on the findings of this Institute of Medicine report, as well as logistical and funding considerations, and the committee is charged with making recommendations about specific mandates. The DVA has no specific plans for any of these research efforts beyond the minimal descriptions given in the law, so the committee is able to comment on them in only the broadest terms.

With regard to the need for a series of scientific "studies on the feasibility of conducting additional scientific research on" health hazards resulting from exposure to TCDD and herbicides used in Vietnam, the research mandate in section 8 of Public Law 102-4, the committee feels that a series of epidemiologic studies of veterans could yield valuable

information if a new, valid exposure reconstruction model can be developed. The committee finds value in continuing the existing Ranch Hand study and expanding it to include Army Chemical Corps veterans. As discussed above, however, these studies should be carried out with some independence from government agencies.

Section 6 of Public Law 102-4 requires the DVA to "compile and analyze, on a continuing basis, all clinical data" that (1) are obtained in connection with examinations and treatment furnished by the DVA to certain veterans, and (2) are likely to be scientifically useful in determining the association between disabilities experienced by these veterans and exposure to TCDD or herbicides. Such a system, called the Agent Orange Registry (see Chapter 2), currently exists. Section 7 of the law calls for the establishment of a system for the collection and storage of voluntarily contributed samples of blood and tissue of veterans who served in Vietnam.

Stored biological samples and clinical data offer some promise for future research efforts. They could, for instance, form the basis for future nested case-control studies of particular diseases. For example, as Vietnam veterans age, studies of the incidence of prostate cancer could compare TCDD levels in stored serum for men with and without the disease. The benefit of such a program is that the cost of storing serum (approximately $50 per veteran per year) is substantially less than that of measuring its TCDD level (almost $1,000 per sample with current technology). It is also possible that new scientific assays or other measurement methods developed in the next 10 to 20 years could be applied to stored serum and tissue, and the resulting analyses might shed light on some of the remaining uncertainty.

To be scientifically valid, however, a study based on stored biological samples or clinical data must be designed with a sampling plan appropriate for the hypotheses to be tested (see, e.g., NRC, 1991). Stored samples are valuable, for instance, in identified high-exposure cohorts, such as the Ranch Hands, the Army Chemical Corps, and perhaps other study groups, so that health effects can be compared to their level of TCDD exposure. By contrast, storage of biological samples or medical records from self-selected individuals, or from those who feel that they are suffering from disabilities due to herbicide exposure, is unlikely to yield scientifically valid information on the health effects of herbicides; any epidemiologic study based on these data would suffer from misclassification bias (see Chapter 5).

Over the last 15 to 20 years, the sampling and storage of human biologic specimens for later analysis in scientific studies have received increasing attention. A 1993 conference on human tissue monitoring and specimen banking, sponsored by the U.S. Environmental Protection Agency and the University of North Carolina School of Public Health, Chapel Hill, explored state-of-the-art banking techniques, design, and ethical considerations. Human tissue banks in the United States and abroad have become a valuable resource for obtaining baseline or historical measurements of toxic substances, and for monitoring and assessing trends in human exposure to environmental or occupational chemicals. Results obtained to date indicate that human tissue monitoring may become increasingly informative, provided that difficult issues of system design, quality control, and ethics are resolved.

Balancing the strengths and weaknesses of stored biological samples and clinical data for research purposes, the committee feels that systems of this sort have scientific value, but only to the extent that they are components of specific, well-designed studies. In the absence of a

clear study design to guide such activities–and without resolution of the design, quality control, and ethical issues–the committee does not recommend the establishment of the clinical data and tissue archiving systems described in sections 6 and 7 of the law at this time.

The final mandate in Public Law 102-4 (section 9) on which the committee must comment calls for testing the serum TCDD levels of Vietnam veterans who apply for medical care or file a disability compensation claim. The purpose of this mandate is not stated in the legislation. If research purposes are contemplated, the committee's discussion about tissue archiving systems applies, and such a program would not be recommended at this time. It is also possible that this program is intended to provide information on individual exposure to TCDD and/or herbicides to aid in individual compensation decisions. The committee cannot make recommendations for DVA policy, but notes that the finding in Chapter 6 that individual TCDD serum levels are usually not meaningful (because of common background exposures to TCDD, poorly understood variations among individuals in TCDD metabolism, relatively large measurement errors, and exposure to herbicides that did not contain TCDD) might apply to this mandate.

OTHER DIOXIN (TCDD)/HERBICIDE STUDIES

Basic toxicologic research on TCDD will further enhance knowledge of its possible human health effects. The committee recommends that basic research be undertaken to investigate possible differences in sensitivity among humans to TCDD-mediated toxicity. Additionally, mechanistic studies focused on identifying possible predisposing molecular or genetic factors for TCDD-associated effects would be highly significant for risk assessment purposes.

It may be possible to learn more about the health effects of the herbicides used in Vietnam by studying occupationally exposed workers than by studying veterans, because the amount and intensity of exposure to TCDD and herbicides experienced by Vietnam veterans were probably small compared to the exposures of production workers, agricultural workers, and herbicide sprayers. Furthermore, records on which to base exposure measures for some occupational groups may be better than those for veterans. Thus, although the committee is not in a position to make detailed recommendations about the conduct of occupational studies, it notes the potential value of such studies to the DVA and other government agencies. In particular, the committee has found that the occupational studies being conducted by the National Institute of Occupational Safety and Health in the United States and the International Agency for Research on Cancer in Europe and elsewhere (see Chapter 7) have contributed substantially to the evidence base for some health outcomes that the committee reviewed, and the committee endorses continuing follow-up and analysis of these cohorts. Making available the individual-level exposure and outcome data from these two studies would be valuable; these data could be pooled and analyzed further with comparable exposure groups and outcome measures. Additional, carefully conducted epidemiologic studies–with adequate sample size to detect elevated associations–of the reproductive history of individuals with occupational or environmental exposure to herbicides and dioxin are also needed.

Studies of the Vietnamese population exposed to herbicides are also possible and potentially useful. These studies might include Vietnamese still in Vietnam or perhaps even those now in the United States. Accurate disease ascertainment and exposure reconstruction may pose difficult problems, however. The actual exposure of this group to herbicides would be extremely difficult to determine accurately because (1) serious problems with recall bias are likely; (2) given war conditions, documents about location during the war in Vietnam are unlikely to be completely available or reliable; and (3) the Vietnamese in question may have relocated in the intervening decades. Current serum TCDD measures may not be practical or relevant for the same reasons discussed above for U.S. veterans. Before significant resources are committed to studies of the Vietnamese population, the committee recommends that feasibility studies of both exposure reconstruction and disease outcome monitoring be conducted.

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ATTACHMENT 2

Appendix C
Methodological Observations on the Ranch Hand Study

INTRODUCTION

Because the veterans of Operation Ranch Hand are among those with the highest exposure to herbicides in Vietnam, because that exposure is well documented by records and serum dioxin measurements, and because the group has been the focus of extensive epidemiological and clinical observation, the Ranch Hand study represents one of the best available opportunities for understanding the health effects of exposure to herbicides in Vietnam veterans. The committee thus reviewed all of the research reports concerning the Air Force's Ranch Hand study in great detail.

The committee is aware of the logistical difficulties involved in such a large and detailed data collection effort, and it applauds the efforts of the Air Force research team in that regard. In addition, the committee also acknowledges the efforts of the Ranch Hands themselves to participate in the follow-up study; they deserve a great deal of appreciation for their efforts. In reviewing the results of the Ranch Hand study, however, the committee identified a number of concerns with the way the data have been analyzed and presented. Ranch Hand analysts seem to have made a good faith effort to be thorough in their analyses and to address a number of potential criticisms in advance, but the report is difficult to read and interpret for a number of reasons (detailed below).

In spite of these defects, the committee recognizes the possibility that extensive reanalysis of the data would not uncover any consistent positive findings, although only actual reanalysis would determine this. The following observations are offered in a constructive spirit, with the hope that they may serve as suggestions for future analyses and reports of the Ranch Hand data and those of similar groups.

PROBLEMS WITH THE REPRODUCTIVE EFFECTS STUDY

The comments that follow focus on the report dealing with reproductive outcomes (AFHS, 1992). The committee feels, however, that many of its observations have somewhat broader applicability to other aspects of the Ranch Hand study as well.

Tabular Presentation of Results

One general concern is that many of the tables and analyses are confusing and inadequately documented. The definitions of column and row labels in the tables relied on prior text so that the tables do not stand alone. There are *p*-values presented without adequate descriptions of the specific hypotheses being tested. Although a thorough reading of the methodology section (Chapter 1) provides the required information, interpretation of the tables would be facilitated by the inclusion of better "stand-alone" documentation in the form of footnotes and expanded row and column headings. Overall, the committee believes that some clarification, some simplification, and more emphasis on estimates of effect than on *p*-values would help the researchers communicate their important findings and would facilitate the appropriate peer review of this work.

Similarly, the committee feels that there is an overreliance on *p*-values in place of simple measures of effect such as relative risks. The executive summary, in particular, contains essentially none of the relevant quantitative data.

Exploration of an Overall Effect

A more specific concern involves the text on page i, describing overall differences between Ranch Hands and control groups. Initial findings, using unverified end points, showed that when looking at births occurring prior to the Ranch Hands' experience in Southeast Asia (pre-SEA), the comparison group had slightly elevated rates of adverse outcomes. When looking at post-SEA births, the reverse was true; that is, the rate of adverse birth outcomes was higher for Ranch Hands. The 1992 report states that subsequent analyses of verified end points confirmed these findings, but the committee could find only one table reporting the findings, and this table did not provide any information specific to particular types of birth defects or several other outcomes.

The data in table 1-16 suggest that some aspect of Ranch Hand service may have caused an increase in rates of birth defects among children born to Ranch Hands, and this should be explored further. However, it is not clear what caused the difference between Ranch Hands and the control group. For this reason, internal comparisons based on different exposure measurements among the Ranch Hands themselves are appealing. The use of multiple definitions of exposure (extrapolated baseline dioxin, current dioxin adjusted for time between SEA experience and dioxin assay, and categorized current dioxin) represents an admirable effort to explore several possible mechanisms. Presentation of the results of these analyses, however, is confusing. Some of the data were analyzed by using continuous dioxin levels, but the presentations in the tables use trichotomized values. It is not very clear whether the results reported refer to the continuous or the trichotomized values, for either past or current exposure (models 1 or 2). One possibility for future analyses would be to report (in addition to what has been done) logistic regression coefficients and odds ratios for the continuous exposure measurements, perhaps by looking at quadratic terms to address any concerns about nonlinear

associations.

Exclusion and Categorization of Data Points

Most of the analyses, especially those using models 1 and 2, excluded the most relevant baseline data, namely those for Ranch Hands whose measured dioxin residues were no higher than background levels. In particular, many of the analyses were restricted to those veterans with current serum dioxin levels greater than 5 or 10 parts per trillion (ppt). This restriction essentially eliminates truly unexposed individuals from the analysis, and makes it difficult to identify positive statistical relationships. It is also arbitrary; other studies reviewed by the committee used various definitions of "background," including 3-4 ppt and 7 ppt.

In model 3, page 1-6, the authors claim that they eliminated people having between 10 and 15 ppt from the "categorized dioxin analysis in an attempt to avoid misclassification of the Unknown and Low categories." There are several potential problems with this strategy:

1. As with the omission of any data from an analysis, it is possible that this biased the analysis. The easiest way to judge whether this occurred would be to redo the analyses with those people included, perhaps as a separate category.
2. An analysis involving categories and not continuous dioxin levels could have been performed using quartiles or quintiles; 0-4, 5-9, 10-14, and 15-19 ppt, or some other categories. No subjects should be discarded from the analyses. These categorical variables could be treated as either nominal scale or ordinal scale in logistic regression models. The specific contrasts between the highest- and the lowest-exposure categories could be accommodated in logistic regression models.

Dioxin levels were unavailable for a large proportion of the cohort. Specifically, 2,278 of 6,792, or 33.5 percent, of the births had no dioxin levels associated with them. The committee could not find any analysis comparing outcomes or other characteristics in those who did versus those who did not have dioxin levels available. The potential for bias clearly exists. At the very least, there is a severe reduction of statistical power.

Correlation of Results Within Subject

The analyses did not seem to account for the reported pair matching of comparisons to Ranch Hands. Some aspects of the study design, including the matching, were not described in enough detail in the executive summary. In addition, the analyses did not consider defects other than the "most serious" one when a child had multiple defects.

The analyses treat data on outcomes for all pregnancies fathered by the same subject as independent binary observations. Especially when restricted to "full sibling" subsets however, there are good a priori reasons to expect that the outcomes within subject are correlated. A large body of statistical methodology has been developed to accommodate such correlated

binary data, stimulated by similar "intralitter" correlations in toxicology. For rare outcomes, it will probably matter very little, but it could be important for more common ones. Tests for such "extrabinomial" variation are available. Because of the high a priori likelihood that extrabinomial variation exists, however, methods that accommodate such variation should be used whenever they yield results different from those obtained by standard methods, which assume independence, even when the tests of that variation do not provide statistically significant results. The generalized estimating equation methods of Zeger and colleagues (Zeger and Liang, 1986; Zeger et al., 1988) are appropriate in such circumstances.

Interaction Terms

There is extensive use of statistical interaction terms in models in the analysis that may have rendered those models difficult or impossible to interpret. Statistical interactions are subtle, but they may be obscuring some of the findings. In general, the concern is that a model containing a main effect for a covariate (such as age of the father), a main effect for dioxin level, and an interaction term, could easily be misinterpreted. If the interaction term is statistically nonsignificant, and if it is highly correlated with dioxin level, which is a very reasonable scenario, the statistical significance for the main effect term for dioxin is uninterpretable. In particular, it is possible that a model with both main effects present, but no interaction term, could reveal a statistically significant effect of dioxin level, but this result could spuriously seem to disappear in the model with the interaction term. This problem is of particular concern for model 2, which includes a main effect for the time between SEA

experience and dioxin level, a main effect for dioxin level, and the interaction. Such a model could obscure any effect of dioxin level.

Analyses of Conception Rates

One intriguing finding in the Ranch Hand report is the increase in the average number of post-SEA conceptions with increasing dioxin exposure. To be able to interpret this result, one needs much more basic descriptive information on how these three exposure groups differ on relevant characteristics, particularly data on year of entry into SEA service. If, as seems possible, those who had the highest dioxin residues tended to enter SEA service earlier so that they had the chance for longer or repeat tours, the higher number of conceptions could be explained by the longer period since their return during which they were "at risk" for conception. It is standard practice in demography to take account of period at risk when analyzing fertility rates in different populations, and the same methods would be appropriate here.

Inclusion of Pre-SEA Births

In one of the models, the analysis included all births whether they occurred prior to or following the subject's SEA experience. There was a main effect term in each model for "pre/post SEA," a main effect for dioxin, and the interaction term between these. The *p*-values reported in these pre/post models apparently represented tests of the interaction terms, which the committee views as of only secondary importance. The hypothesis being tested is whether the effect of dioxin (if any) is the same for pre-SEA births as for post-SEA births. Presumably, if an effect of subsequent dioxin exposure on pre-SEA births were detected, this would be a result of bias in the study design, confounding, or both. Although this hypothesis is of some interest, the report did not appear to include an estimate and test of the effect of dioxin in the post-SEA births for these models. The presentation of the *p*-values conveys the impression that the dioxin effect is nonsignificant. Although this may be true as well, that is not what the committee understood those *p*-values to be testing, and it was not completely clear from the tables exactly what the *p*-values do represent. It would be preferable to analyze only post-SEA birth, create a history variable (History of adverse reproductive outcomes prior to SEA experience? Yes or no?), and include that variable in the logistic regression model.

Lack of Documentation of Algorithms for Adjustment for Covariates

On page 1-7 the authors say, "When appropriate, analyses were adjusted for as many as 8 covariates," but they do not state the criteria for deciding when it was appropriate. In order to interpret the results, it is necessary to know how the decision was made as to which covariates were or were not included in any particular analysis.

Table 3-21 (page 3-22) provides an example: The unadjusted model shows no significant association between (log) initial dioxin and miscarriages. In the adjusted analyses, a significant (or nearly significant) effect of service occupation is found. Since service occupation was highly correlated with dioxin levels, it is unclear how to interpret the finding of no effect of dioxin in the adjusted models. Adjustment of an exposure variable for a highly correlated variable that may, in fact, represent a surrogate measure of exposure is not generally recommended and may have obscured a positive relationship.

SUMMARY OF STUDY

In summary, several issues need to be addressed in future analyses of the Ranch Hand reproductive effects data. The technical issues raised above, particularly the restriction to those with current dioxin levels above background and the potential misapplication and/or misinterpretation of interaction terms, are of concern because of the conclusions drawn from them. The problems with the analyses could lead to apparently inconsistent findings with regard to the estimated effect of dioxin on outcomes. These apparent inconsistencies might or

might not reflect the actual situation. Thus, the conclusion drawn in the report that the inconsistent findings do not support an effect of dioxin may not be valid, since the inconsistencies may simply reflect problems with the analyses. On the other hand, it is very possible that reanalysis of these data, according to the recommendations listed above, would not lead to any substantively different conclusions.

Further exploration of the overall differences between Ranch Hands and the comparisons should also be pursued. Some aspect of the Ranch Hand experience seems to have increased the risk of fathering children with birth defects, but the implications of this finding are unclear. If reanalyses of the dioxin data still show that dioxin is not associated with increased risk of birth defects, a great deal of careful exploratory analysis will be required to sort out exactly what the cause of the increased risk might be.

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Statement of
Richard A. Albanese, MD
before the
Senate Committee on Veterans' Affairs
21 October 1993

I will address the conduct of dioxin studies, dioxin dose assessment, and elements of data analysis. The opinions expressed are my own, and are not necessarily those of the United States Air Force.

The Conduct of Studies. Occupational, environmental and public health questions are often associated with conflicting public and private interests and values. Therefore, in my view, it is very important that procedures and customs be put in place so that medical scientists studying these questions are well protected from the appearance and possibility of genuine conflict of interest. With respect to dioxin studies in veterans and other similar studies, I recommend three actions:

(1) routine use of quality, balanced, fair peer review,

(2) easy availability of data used to compose reports,

(3) development of programs supporting academic freedom in occupational, environmental and public health research facilities.

The first two of these recommendations are similar to but extend those of the recent National Academy of Sciences (NAS) report (titled "Veterans and Agent Orange: Health Effects of Herbicide Used in Vietnam," 1993). The third recommendation reflects solely my own thinking.

Peer Review. Published reports with an important bearing on veteran or general public health should have carefully balanced peer review. The peer review group should be balanced by containing contingents from all interested parties. In the case of dioxin, there should be governmental representatives, academic representatives, participants who actively and empathically communicate with veterans' groups, and representatives of the general public who can consider economic and health concerns. The peer review group should examine scientific methods and evaluate results for scientific rigor. Evaluation of complex health data has a subjective dimension; therefore, the peer group should ensure that the complete spectrum of scientifically tenable opinions is represented fairly.

My personal scientific opinions coincide largely with those expressed in the NAS report. I feel comfortable with the fact that the NAS review group accepted statements from several sources including government scientists and veterans. However, I believe that the report would have been further strengthened had the review group contained one or two government scientists,

veterans representatives, and an economist, sociologist, science historian or clergy to represent the general public point of view.

The statement was made in the NAS report that the committee members had no conflict of interest regarding herbicide issues. Freedom from conflict of interest is very difficult to reliably ascertain. How was the determination of no conflict made? The report offers as evidence the fact that none of the committee members had made public statements about herbicide or dioxin issues. Are we to assume the NAS group is biased now that they have published their report?

It is my understanding that the disciplines of psychology and sociology would assert that the important question is not the presence or absence of bias in a group rendering an opinion. Rather, the important question concerns the degree to which the individuals in the group hold opinions that are poorly supported by data (that is, are biased), and the degree to which the individuals involved are unable (or able and willing) to examine their assumptions. I recommend that review groups include representatives of interested groups even if this means the presentation of minority statements. Inclusion of diverse opinions leads to the strongest scientific progress in the long run. Active participation of many viewpoints reduces bias. I recommend that academic, industrial, government, veteran and general public groups remain actively engaged in the dioxin/herbicide issue.

Data Availability. If a peer review group gets too large, it becomes logistically unmanageable and inefficient. Thus, it is unavoidable that important scientific disciplines and capabilities are not represented. Also, it is impossible to anticipate future improvements in statistical techniques or other scientific advances. I would like that data from important health studies be made available so that interested scientists can try their own analyses on the data, and so that statistical and scientific advances developed in the future can also be applied. Therefore, I recommend that data from major health studies be provided to scientists for independent analysis at their own expense. I propose that the data be made public in this way after the initial report is issued, and that it be provided at a moderate price reflecting the actual cost of computer formatting.

Academic Freedom. Unconscious desire to please the supervisor, and the supervisor's unconscious desire to protect the institution can lead to sub-optimal scientific performance. This problem is particularly serious in hierarchical research settings. I believe that the appearance and possibility of inappropriate influence can be minimized in government research, in government funded research, and in industrial research if formal policies are articulated and practiced by example by institutional leaders. These policies must firmly establish that

scientists have the responsibility to exercise full academic freedom. That is, scientists are to act in a manner fully independent of all non-scientific policies or interests. This policy on academic freedom should be articulated clearly by institutional leaders at regular intervals, and should be followed by intermittent inquiries permitting confidentiality. Diverse viewpoints should be consciously encouraged. In occupational, environmental and public health science, as in so many other settings, diversity is strength, and tolerance for diversity must be cultivated.

Dose Assessment and Data Analysis. In my opinion, serum dioxin measurements and tissue measurements are important components in the mosaic of dioxin exposure assessment. Great care must be exercised when back-projecting from a few values taken at different times from a given individual. There must be a continued emphasis on the conditions of exposure, and biological factors that influence dioxin metabolism and excretion. Data analyses using dioxin measurements must incorporate uncertainties associated with that measurement - so-called measurement error, and issues of misclassification must be addressed.

Future analyses of dioxin effects in veterans or in other occupationally or environmentally exposed individuals should more fully exploit the increasing knowledge concerning the mechanism of action of dioxin. I refer particularly to aryl hydrocarbon hydroxylase activity, and to the possibility of free radical intermediates. Data analyses must be grounded as firmly as possible on basic knowledge concerning dioxin and knowledge of the disease processes that it may cause. An important example to me is the recent Ranch Hand birth defects report which finds an excess of birth defects in the exposed group but does not find evidence to support a dose-response association. Important statistical analyses in that report assume a model that forces birth defect rates to drop to zero as the serum dioxin level goes to zero, neglecting natural background rates. In my view, this biologically incorrect assumption may have seriously skewed inference.

Conclusion. In summary, governmental laboratories, government funded efforts and industrial efforts are pivotal in occupational, environmental and public health issues. The academic freedom of scientists can be assured by sensible programs of peer review, publication of data, and support of intellectual diversity in the research facility. Excellence in dioxin studies will depend on careful dose assessment without over-emphasis of serum or tissue levels, and on the detailed molecular and medical understanding of dioxin effects and disease processes guiding the analysis.

I sincerely thank the United States Air Force Armstrong Laboratory for financially supporting the travel associated with this testimony, and for providing a quality environment for both doing science and thinking about science.

Testimony of Peter C. Kahn
before the Committee on Veterans' Affairs,
United States Senate
November 2, 1993

Mr. Chairman and members of the Committee, thank you for the opportunity to appear here today. In testifying I wish to emphasize that I do so as an individual, speaking for myself rather than as a representative of my University or any other organization.

We are asked to address many questions today on the directions of future research into herbicide exposure and veterans' health, all of them complicated. There is not time to discuss any of them in depth let alone all of them. The best I can do is to comment on a few and to make myself available to be of assistance both today and hereafter.

The Institute of Medicine's Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides have done an honest, workmanlike job. Having attempted my own literature review over the years, I have a good idea of just how hard it is to make sense of a bewildering array of often conflicting studies in a wide range of different fields. I say this to emphasize that whatever criticisms I have of their report are minor and should not be blown out of proportion.

One of the Committee's principal conclusions was that assessment of exposure to herbicides is the weakest link in the epidemiological work done on veterans to date. Fully five of their six specific recommendations concern the rigorous identification of exposed and unexposed groups of people and among the exposed, establishing the degree of exposure. They are right. Unless this can be done, no valid health study is possible, for misclassification errors will obscure any real associations which may exist between exposure and disease.

Much work in the field has suffered from this problem, especially work on the veterans. The realization of the need for good exposure assessment, in fact, motivated most of the studies in which I have participated going back to 1981, when planning for New Jersey's project began. Given the limited resources available to us, we felt an exposure study would be the best contribution we could make. The measurement of TCDD levels seemed a reasonable approach at the time, so that's what we did.

I mention this to emphasize that although I participated in the development and validation of the methods currently in worldwide use to measure blood serum dioxin levels, I agree fully with the Committee's recommendation to develop exposure data based on a broad range of historical records from the war. We advocated exactly such an approach in our paper back in 1988. The best work in this area to date, by the way, is certainly the Stellmans'. Praise should have been heaped upon them for it instead of the vilification which has more often been their lot.

Blood measurements do have a role to play, which the Committee point out, as an adjunct to and possible validation of records based exposure estimation. They are right also in noting how thin our understanding of dioxin toxicokinetics is. This means we have little knowledge as to how variable the excretion rate may be from one person to another or whether women's bodies handle chemicals of this sort as men's do. There are other unknowns, as well, whose penetration is necessary to the fully effective use of the method for human benefit. I have, in addition, some detailed technical suggestions for which this is not the appropriate forum.

I disagree with the IOM's Committee on the clinical use of blood serum measurements. They are no different from any other laboratory test which might - or might not - guide physicians in diagnosis and treatment. It is true, the test is expensive and time consuming. So are many others - a detailed immune function screen, for example. It is also true that a negative answer, i.e. a low current level, leaves one hanging, for one cannot know from such a result whether the patient always had a low level or whether it dropped back to normal in the time since last exposure. Like any test, it depends for its clinical usefulness on the physician's knowing its strengths and weaknesses. If this means educating doctors about it, so be it. That done, it should be the physician's and patient's joint decision, and if they decide it would be useful, the VA should pay for it whether or not the referring physician is a VA doctor. There are both moral and practical reasons for the VA to do so.

With respect to archiving samples and compiling clinical data from veterans who present themselves at VA facilities - the Agent Orange Registry, for example - I agree there is little to be gained in the absence of a clear study design, and the data compiled without such a design can be - and have been - put to pernicious use. The General Accounting Office's scathing comments some years ago on quality assurance in data entry to the Registry are pertinent here, too.

In order to develop methods of reconstructing exposure from military records, it will be necessary to rejuvenate the Joint Services Environmental Support Group. Years ago it became expert in sifting records and will certainly be needed to do so again. It has fallen on hard times, though, and will not be able do what will be needed without an injection of money for staff and facilities. Clear and continuing administrative support from the Defense Department will also be needed for the ESG and for other of the IOM's recommendations.

The IOM discusses briefly the usefulness of research in Vietnam. It would most certainly be helpful, and research cooperation between that country and the United States already exists. I suggest it be expanded both within the U. S. and to include staff from the International Agency for Research on Cancer, an office of the U.N. They too have significant competence from work in Vietnam.

Finally, the history of the Agent Orange controversy has been contentious, to put it mildly. For this reason, I cannot agree more strongly with the IOM's recommendation that all new work be organized, conducted, and evaluated by non-Federal entities. Above all, keep the VA out of it, and, with one exception, keep the CDC out, too. Likewise, the Agent Orange Working Group, if it still exists, should simply be abolished. This is not the place to rehash a sorry history, but if any of these agencies have significant roles, the public will not accept the results, and many scientists who have a great deal to contribute will have nothing to do with it.

The exception in the case of the CDC is the dioxin lab. It is a good lab. In fact, it is among the world's best. While I often disagree vigorously with their interpretations of data, I have never had a reason to question the quality of their measurements or their honesty in presenting them. The lab could well be useful in doing body burden measurements. There are other labs in the country which should take part, as well.

As a country we have treated the veterans shabbily in many ways, the Agent Orange controversy being but one of them. By failing to do the necessary research years ago, we brought discredit unfairly onto science and onto scientists as a group. We can't afford that, for if science is discredited, good people will not go into it, and our civilization will suffer. We have weakened our democracy as well, for faced with the spectacle of the Agent Orange controversy, people lose faith in our governing institutions. We have a chance now do redeem some of that, but only if we do it with vigor, steadiness of purpose over the long term, and intelligence.

SENATE COMMITTEE ON VETERANS' AFFAIRS

HEARINGS ON AGENT ORANGE AND DIOXINS

10:00 A.M.
TUESDAY, NOVEMBER 2, 1993
ROOM SR-418 RUSSELL SENATE OFFICE BLDG.
WASHINGTON, DC

TESTIMONY OF

ARNOLD SCHECTER, MD, MPH

VIETNAM BASED AGENT ORANGE RESEARCH AND RELATED ISSUES

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Thank you for inviting me to speak today. As a Vietnam era veteran of the U.S. Army Medical Corp from 1967 to 1969, the subject of Agent Orange and dioxin exposure with the potential for serious health effects is one which very much concerns me.

Also, to introduce myself, I am a physician-scientist who has worked exclusively on dioxin related issues for the past ten years. As such, I have been privileged to serve in recent years as a peer reviewer, consultant, or advisor on dioxins, dibenzofurans, and PCBs to the World Health Organization, the U.S. Environmental Protection Agency, the Agency for Toxic Substances and Disease Registry of the U.S. Public Health Service, and the National Institutes of Health. Since 1981, my work as a academic public health physician researcher has involved studying dioxins in the environment, dioxin exposure assessment in patients, and dioxin human health effects.

In a presentation in 1983 my colleagues and I were the first to report that dioxins were found in surprisingly high levels in all Americans in the general population, not just in Vietnam veterans or other special populations. We also demonstrated, for the first time in America, that analyses of blood and fat tissue can identify elevated dioxins and dibenzofurans in some workers exposed to these chemicals.

Beginning in 1984, my colleagues and I have studied Vietnamese exposed to Agent Orange and dioxin in the south of Vietnam and those not exposed in the north of Vietnam. We also conducted Agent Orange exposure studies on American Vietnam veterans from Massachusetts and later Michigan.

I am providing this committee copies of the detailed report on our research findings and my research and policy recommendations which I presented to the National Academy of Sciences last year for use with their Agent Orange study. We were pleased to find some portions of this work used in the final report. In addition, I am leaving information on our Massachusetts and Michigan Vietnam veteran studies and some of our published research on Agent Orange in Vietnam along with published Vietnamese Agent Orange research.

Our findings this past 12 years were quite straight forward, and with respect to American veterans, are similar to findings in the New Jersey studies, and some federal government studies which followed our earlier work.

I. SUNY HEALTH SCIENCE CENTER DIOXIN RESEARCH FINDINGS

A. **Some American Vietnam veterans, including ground troops, have elevated blood and fat dioxin level (of 2,3,7,8-TCDD) from Agent Orange, as long as 26 years after leaving Vietnam.** Elevated dioxin levels are most easily found in some Agent Orange sprayers and those who directly handled the defoliant.

B. **Dioxins can be found in semen as well as in blood of veterans and presumably others.** Therefore, the possibility exists that elevated dioxin in semen of veterans could contribute to adverse reproductive outcome in their children as has been hypothesized as a mechanism for male-mediated adverse reproductive outcome. Further work to follow up this finding from our Michigan study is indicated.

C. **Since 2,3,7,8-TCDD is gradually eliminated from the body over time, we estimate that unless dioxin exposure in Vietnam was relatively high (i.e. blood lipid level of over about 50 parts per trillion), we can no longer document dioxin exposure from Agent Orange by blood tests at the present time.** Thus, a "positive" blood or fat test for elevated TCDD can be useful to establish exposure and intake, but a "negative" or non-elevated finding should be interpreted as part of the total evaluation to be made by a qualified, trained and experienced physician.

D. **Even Americans with no special exposure currently have detectable levels of dioxins, dibenzofurans, and PCBs in their blood.** The primary route of exposure is food, especially meat, fish, and dairy products. Infants can be exposed to these toxic chemicals transplacentally and through nursing. Thus all Americans are subject to potential health risks from dioxins.

E. **Elevated dioxin tissue levels from Agent Orange can be found much more easily in Agent Orange exposed Vietnamese living in the south of Vietnam than in American veterans.** This is not surprising, since there were 17 million Vietnamese living in the south of Vietnam when the 12 million gallons of Agent Orange were sprayed. The Vietnamese exposure is far longer than the one or two year tours of duty that American veterans served.

II. RESEARCH RECOMMENDATIONS:

A. GENERAL

Health research on Agent Orange is time-limited. The best biomarker of exposure, measurement of blood or fat dioxin levels, is only helpful for a limited period of time after exposure. The longer we wait, the less we will learn.

University-based American medical research traditionally leads to high quality results and should be used for most Agent Orange-dioxin research. Scientific and policy advisory committees can serve a useful function if well informed and impartial but original research comes from individual scientists. Usually, the most original new ideas are frequently most difficult to "sell" to conservative funding agencies. There is an urgent need for many relatively small but innovative, original research projects, since we do not know in advance which will be successful.

1. N.I.H. extramural investigator initiated grants or contracts should be effective mechanisms for funding a series of relatively small, focused research projects in Vietnam and in the U.S. which will benefit American veterans with respect to Agent Orange knowledge.

2. E.P.A funded grants and contracts could also serve to fund university and medical school research projects.

3. There is also precedent for special government offices to coordinate and implement research projects on a given health problem. Former President Nixon established the Special Action Office on Drug Abuse Prevention (SAODAP), out of the Executive Branch at the New Executive Office Building and headed by a former professor of psychiatry, Dr. Jerome Jaffe. This office, in its relatively brief life, organized and coordinated major innovative projects in drug abuse rehabilitation and treatment. Such an office could be established to serve a similar function for Agent Orange.

B. VIETNAM RESEARCH:

Based on over a decade of Vietnam-U.S. collaborative study, my colleagues and I strongly support the recent Institute of Medicine - National Academy of

Sciences report where it suggests Vietnam-based collaborative research on Agent Orange and health. My associate, Dr. John D. Constable of Harvard Medical School, began his U.S. government sponsored Agent Orange research in 1970. In my experience working in Vietnam beginning in 1984, I have found the Vietnamese to be well organized in their Agent Orange research teams and very cooperative. Regardless of diplomatic relations between our two countries, it seems to me that such collaboration can only benefit American Vietnam veterans, as well as our former allies in the south of Vietnam, and all others exposed to dioxins, which includes all Americans, especially nursing infants.

1. Exposure Assessment

There is an urgent need to determine where in Vietnam Americans were more or less likely to have an intake of Agent Orange. Dioxin blood or adipose tissue measurement is a very powerful medical tool, although not perfect, it is somewhat expensive and slow. At 1000 - 2000 dollars per analysis, systematic measurement of pooled blood specimens from Vietnamese, can be used to develop methods to predict the likelihood of our veterans' Agent Orange intake in a given area. Vietnam offers the best opportunity to determine exposure assessment by geographical areas for Americans.

2. Health Consequences

Vietnam offers the best opportunity to determine health consequences of Agent Orange exposure for a variety of reasons:

a. **Large numbers of Vietnamese, perhaps millions, had substantial intake of dioxin from Agent Orange.** The highest measured human milk TCDD value anywhere in the world, as well as the highest measured from Agent Orange exposure is 1,500 parts per trillion (ppt) in milk lipid from a Vietnamese woman, which compares with 3-5 ppt found in U.S. general population specimens today. In contrast, with average TCDD levels around 1 ppt, most of the population in the north of Vietnam, now 36 million, has had little or no exposure to the dioxin of Agent Orange or other dioxins for that matter. Although unfortunate for those exposed, these distinct populations are unique and ideal for population based health studies.

c. **The Vietnamese did not serve only one or two years of duty in Vietnam, but lived there during and after the spraying.** They live on the land and eat the food of their country. Therefore, their intake of dioxin from Agent Orange should usually be higher than that of Americans.

d. **Vietnamese men, women and children were exposed to Agent Orange.** We can obtain information on health effects of all three groups more readily in Vietnam than any other country in the world. Our data reported in the World Health Organization "Field Studies" found that only in Vietnam were there geographical regions with higher and lower levels of dioxins. The south was higher and the north lower, in humans and in the environment.

C. EPIDEMIOLOGY

There are a number of very important health issues of concern. It should be possible to determine more easily in Vietnam than anywhere else in the world, at what levels of Agent Orange exposure, if any, there are increases of:

1. Cancers
2. Immune deficiency
3. Adverse reproductive outcomes, including
    a. spontaneous abortions
    b. fetal death *in utero*
    c. malformations
    d. cognitive or behavioral deficits in offspring
    e. endocrine disorders in offspring
4. Central nervous system damage
5. Peripheral nervous system damage
6. Endocrine disorders, including diabetes, sexual disorders and thyroid disorders
7. Liver damage
8. Skin disorders
9. Other illnesses

The importance of such research cannot be overemphasized. The unique mixture of chemicals in Agent Orange was sprayed in Vietnam, which is where our veterans served. Other conditions in Vietnam may also have contributed to illness. If this is the case, Vietnam offers the best place to determine this. Health effects may be from the dioxin, 2,4-D, 2,4,5-T or a combination of these constituents of Agent Orange.

We may possibly find that there is no need for concern about Agent Orange exposure for some or many veterans because they either were not exposed or because their exposure was too low for concern. If this is the case, these veterans and their families should be informed accordingly and will hopefully be offered some reassurement. If we find cause for concern for some of our Vietnam veterans, then they can be medically followed to prevent or for early detection of illness, hopefully followed by treatment and cure. Also, compensation could more fairly be determined.

C. BASIC AND CLINICAL RESEARCH

There are many simple but important research projects which must be performed to help Vietnam veterans and others exposed to dioxins. These include:

1. Determination of the kinetics of dioxins in humans.

2. Determination of extrapolation of cancer ratios for estimated levels of dioxins in target organs for illness, as liver, lung, etc, from blood or fat tissue levels. Measurement of dioxins in autopsy tissues can rapidly provide this data.

3. Determination of consequences of wasting, as from cancer or from AIDS on blood or fat dioxin levels, to make possible determination of dioxin dose for a patient with terminal cancer, for example, who has lost most of his or her fat tissue.

4. Determination of dioxin levels in semen, and comparison with blood or fat tissue levels, to determine if it is possible to extrapolate from blood to semen levels.

5. Studies on reproductive consequences of semen containing elevated levels of dioxins.

6. Investigations of methods to reduce body burdens or levels of dioxins in individual patients where this might be indicated.

7. Reproductive studies on outcomes in children when exposed mothers' and fathers' dioxin levels and dose are determined.

III. POLICY RECOMMENDATIONS

A. COMPENSATION

Where there is a probability of illness being partially or fully causally related to exposure to Agent Orange and dioxin, the veteran and his or her family should be compensated. For example, every animal study on cancer initiation or promotion shows that dioxins are carcinogens. Many human studies have the same findings. Various types of cancer and organs have been involved. This evidence is now overwhelming. As a matter of policy if not science alone, veterans should be given the benefit of the doubt.

I recommend dioxin blood analyses be paid for by the Veterans Administration for those veterans or other patients possibly exposed to dioxins where it is indicated by competent medical judgement of the attending or consulting physician. Unfortunately, at present, it is rarely possible to get third party payment from the Veterans Administration or any health insurance carrier for such medical tests.

B. EDUCATION

Health care providers and veterans should have up to date education on what is known and not known about dioxins and Agent Orange. Since veterans frequently do not have much faith in the credibility of government, unfortunately, including the Veterans Administration or the Centers for Disease Control, universities and medical schools probably can best prepare such documents and update them as needed. Videos as well as written matter should be prepared.

C. RESEARCH IN VIETNAM

Research must be done in Vietnam by joint U.S.-Vietnamese medical research teams as well as on American veterans and others exposed to dioxins in order to most effectively and most quickly help American Vietnam veterans. The cultures of Vietnam must be understood and respected as well as the medical science if such research is to succeed. For example, a Vietnamese businessman of Chinese extraction in the Cholon portion of Saigon City, now Ho Chi Minh City, is as different from an ethnic Vietnamese Hmong tribespersons of the Central Highlands or residents of rural northern Vietnam

as is an American from Tupelo, Mississippi from a typical American from rural Maine or from New York City. Anthropologists, and sociologists could possibly play as key a role in Agent Orange health research as physicians, epidemiologists and other scientists.

D. FOREIGN EXPOSURE INCIDENTS

There are other closely related incidents which resemble Agent Orange in Vietnam. They include the Yusho rice oil poisonings in Japan and also in Taiwan (Yucheng), and the Russian men, women and children exposed to dioxins from chemical manufacture in Ufa, Russia. American research money spent in these countries will speed up our knowledge of dioxin effect in humans and help our veterans. We can not, for moral, ethical or legal reasons dose humans with toxic chemicals so we must learn from accidental contaminations wherever they occur.

E. TIME

The last American veteran served in Vietnam in 1975. Agent Orange spraying stopped in 1970. If research is not done promptly, with subsequent policy changes for compensation and for medical treatment, American Vietnam veterans will have died, of disease related or not related to Agent Orange, or of old age. It has been said that justice postponed is justice denied.

As a former Army Medical Corp physician during the Vietnam war, I would urge you to see that at least several million dollars is spent each year, beginning at this time, at American universities and medical schools to provide an answer to our Vietnam veterans as to the relation of Agent Orange and health.

We are spending many millions of dollars each year as we should, to resolve the question of our 2,000 MIA-POWs. It is only right to not forget our 3 million veterans potentially exposed to Agent Orange and spend a reasonable amount of money to resolve their legitimate questions also.

Again, Thank you for inviting me to be here.

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AGENT ORANGE, DIOXINS AND VIETNAM

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INTRODUCTION

This paper provides a selected summary of more than a decade of dioxin research, primarily in the field of exposure assessment. Although a primary focus has been on research pertaining to Agent Orange and dioxins in American veterans,[1-6] our research on dioxins in Vietnam, because of its general and specific relevance to the issue under consideration, is also covered in some detail.[7-24]

Since 1970, elevated 2,3,7,8-TCDD (TCDD), the dioxin characteristic of Agent Orange, has been readily found in varying degrees in tissues of adults residing in southern areas of Vietnam that had been sprayed with Agent Orange.[7-10,13,16-18,20-24] The same dioxin pattern characteristic of Agent Orange was also found in some environmental samples from the south of Vietnam, including riverbed silt, wildlife, and food.[11-12,14-15,19] In the north of Vietnam, the pattern and low levels of dibenzo-p-dioxins and dibenzofurans, or for brevity, dioxins, measured in a congener specific pattern was not characteristic of Agent Orange, or even of industrial dioxin contamination, as is seen in other countries. Dioxin levels are quite low in the north of Vietnam in all matrices sampled to date, human or environmental.

In pilot studies conducted on Vietnam Veterans as part of the Massachusetts and Michigan Agent Orange Projects, some ground troops and sprayers still had elevated TCDD from Agent Orange over 20 years from the time of exposure.[2-6] By our calculations, only tissue levels above approximately 44 parts per trillion (ppt) of TCDD at the time of service would cause tissue levels to be elevated in Vietnam Veterans at the present time. By way of comparison, we and others have shown that the average American adult has a TCDD level of 3-4 ppt in blood lipid.[22]

Using improved analytic techniques, dioxin-like polychlorinated biphenyl (PCB) congeners were also found in the blood of all Americans studied, including veterans in the Michigan Agent Orange study.[5,6] These PCBs increased the body burden of dioxin-like chemicals above the 20 to 40 ppt "dioxin toxic equivalents,"[25-27] reported in the current literature by ourselves and others in blood for the general population. This means that PCBs increase, and perhaps double the total dioxin toxicity in humans. Therefore, an additional intake of dioxin above background levels in Vietnam or elsewhere may potentially have greater significance for adverse health outcomes than would such an intake if other toxic chemicals were not already present in an individual.

In the Michigan study, we have recently also been able to identify dioxins in semen for the first time. This finding may be of significance in male mediated adverse reproductive outcome.[28,29]

Our research suggests that environmental and health studies in Vietnam offer the best opportunity to find answers to questions regarding the relationship between Agent Orange exposure and health. Vietnam has very large populations of men, women, and children, some with higher and also some with lower levels of Agent Orange exposure and dioxin exposure; a long period of time has elapsed since first exposure; and there are established Vietnamese scientific and administrative organizations willing and eager to cooperate with scientists from other countries. To resolve questions related to the health effects of Agent Orange and the Vietnam War as expeditiously as possible, it is recommended that a Special Action Office be established with authority from the White House to focus exclusively on these issues, as has been done under previous administrations for matters of urgent public health concern, such as drug abuse in the Nixon administration.

BACKGROUND

I should briefly like to introduce myself and my work in the field of exposure assessment of dioxins and structurally related compounds.

I am a physician and have been a tenured Professor of Preventive Medicine at a State University of New York (SUNY) medical school branch campus in Binghamton, New York since 1979. I have served as a consulting or reviewing scientist for the Environmental Protection Agency on their "Bioavailability of Dioxins" project and publications; the "Human Health Assessment of Dibenzofurans" project and publication; and the recent "Human Tissue Levels of Dioxins and Dibenzofurans" project and publication. I have served as an advisor to the World Health Organization (WHO) on consultations and projects that consider techniques of measurement of dioxins and related chemicals in human tissues and have also participated in WHO field studies of dioxin levels in various countries, sharing our findings on human tissue levels in the United States, Vietnam, Thailand, Cambodia, India, Russia, and a number of other countries with WHO.

During the past few years I have served as a scientific peer reviewer for the Agency of Toxic substances and Disease Registry the *Toxicological Profile for*

Dioxins, the *Toxicological Profile for Dibenzofurans*, and most recently the *Toxicological Profile for Polychlorinated Biphenyls*. I have been involved in Agent Orange research with the Ministry of Health in Vietnam, making annual visits since 1984. On three occasions since 1988, working in various locations from Moscow to Siberia, I have performed collaborative dioxin research with a number of Institutes of the Academy of Sciences in the former Soviet Union.[19,22] My colleagues and I coordinated the Massachusetts Agent Orange and Dioxin in Human Tissue Study[2-4] and we are currently completing a similar but larger study for the State of Michigan.[5-6] I have served on the American Legion Scientific Advisory Committee, consulting on Agent Orange and dioxin issues. I have also served as an expert on dioxins and related chemicals for the Environmental Defense Fund.

I work full time in the dioxin field, especially in assessment or characterization of exposure to dioxins and related congeners, but also in attempting to characterize biological response, and also study certain other biomarkers of sensitivity or reaction, particularly those which can be characterized by the use of ultrastructural analysis of human and animal tissues.

My first involvement with polychlorinated dioxins (PCDDs) or dioxins and polychlorinated dibenzofurans (PCDFs) or dibenzofurans began in 1981, when I responded to a polychlorinated biphenyl (PCB) transformer fire in Binghamton, New York, in my capacity as (part-time) County Health Commissioner. [30] Dioxins and dibenzofurans had been produced during the fire by pyrolysis of chlorinated benzenes and PCBs in the transformer fluid. It was decided to test potentially exposed workers' blood and adipose tissue for dioxin and dibenzofuran congeners. Dioxins and dibenzofurans are chemically and toxicologically nearly identical so both were considered important in exposure assessment as related to adverse health outcome. Such human tissue measurement of workers exposed to dioxins and dibenzofurans had not previously been attempted in the United States, nor had dioxin and dibenzofuran levels in control or general population blood or adipose tissue yet been attempted or reported in the United States.

The testing of potentially exposed cleanup workers in Binghamton revealed elevated congeners in some workers of certain PCDD/Fs to which workers had been exposed, while other workers' levels were not elevated above general population levels.[31-33] There can be a number of explanations for this finding, but one of the most important is that the potential for exposure is not always the same as actual exposure and elevated tissue dose. Other possible explanations

involve kinetics, insensitivity of the measuring tool, especially at low levels of exposure, or after the passage of time, and so forth.

The Binghamton study also found and reported for the first time surprisingly high levels of dioxins and dibenzofurans in the general population, in blood and adipose tissue, about 1,200 ppt, total.[31,32] Until this report in 1983, it had been assumed that the general population was not exposed to dioxins, and that only Vietnam veterans or other special populations were exposed to and had elevated dioxin body burdens.

From this early work it became clear that epidemiology studies involving Agent Orange or dioxin exposure were frequently subject to serious misclassification error if they assumed dioxin intake, for example, from Vietnam Service of any kind, without exposure history and tissue measurement in a timely fashion for determination of the dioxins in question. Insofar as the assumption that the general population in the United States was not exposed to dioxins was incorrect, there was also serious misclassification in epidemiology studies which made that assumption, including many if not all dioxin health studies up to that time.

VIETNAM

Shortly after beginning work on developing measures of exposure to dioxins I was invited to Vietnam by Professor Hoang Dinh Cau who was a Vice Minister of Health at the time. The 1984 visit to Vietnam, the first of many yearly visits, was of interest in a number of ways. I learned that the government of Vietnam had established a high level coordinating committee to study the consequences of chemicals used during that war because of concern about the health effects in Vietnamese civilians and soldiers from chemical exposure from what we call the Vietnam War and what they refer to as the Second Indochina War. This committee is now referred to as the 10/80 Committee to Study the Consequences of Chemicals used during Wartime. It was founded in October, the tenth month of 1980, hence the name 10/80 Committee. It is presently based in Hanoi at the Hanoi Medical School, with local committees throughout Vietnam. A number of Vietnamese and international cooperative research projects have been sponsored by the Committee, and two conferences have been held which have published proceedings.

The Chairman of the Committee is Professor Hoang Dinh Cau, former Vice Minister of Health and former Dean of the Hanoi Medical School. The Secretary is Professor Le Cao Dai of Hanoi Medical School. Dr. Nguyen Ngoc thi Phuong, Director of the Obstetrics Hospital in Saigon City in Ho Chi Minh City (HCMC), is a well known physician and scientist who has performed key studies sponsored by the 10/80 Committee and the Ho Chi Minh City Provincial Health Department in the South. Another key physician and scientist is Dr. Pham Hoang Phiet of Cho Ray Hospital in Saigon City, HCMC Province. I hope your committee will invite these key participants here to discuss directly with you their clinical perceptions and findings from the Vietnamese Agent Orange studies.

To summarize the Vietnamese studies, a number of epidemiology studies have been conducted which suggest to their authors that, following Agent Orange exposure, there may be an increase in adverse reproductive outcome, childhood deaths and cancers of several types, liver and soft tissue sarcoma among them.[28,29 34-43] Vietnamese studies have also reported increases in congenital malformations, spontaneous abortions, and excess childhood deaths which the authors believe are related to Agent Orange exposure. There have been clinical impressions of a possible increase in hydatiform moles and choriocarcinoma following Agent Orange as compared with controls, but these conditions are common in Southeast Asia in general, even where Agent Orange has not been used. In my judgement, the evidence is insufficient to come to firm conclusions at the present time about dioxin related health effects in Vietnam.

I share the impression of most knowledgeable Vietnamese that some of these studies are suggestive, but further work needs to be done. Previous studies should be repeated, and new health studies performed, controlling for possible confounders and estimating Agent Orange exposure in cases and controls by methods which include blood dioxin determination of all congeners, with subsequent conversion to total dioxin equivalents. The Vietnam studies, like studies in any country, vary in sophistication. They should be considered for what they are: Studies conducted with great expenditure of time and energy by intelligent and hardworking physicians, scientists and public health workers in a very poor country just emerging from decades of war. The studies show dedication to finding answers and the willingness to share findings with foreigners. They also demonstrate a strong desire to work with scientists from other countries to determine the extent of human health effects from Agent Orange.

Our own findings in Vietnam show that in the south of Vietnam where 35 million people now live, it is very easy to find Vietnamese with evidence of elevated 2,3,7,8-TCDD, the dioxin characteristic of Agent Orange, in a pattern strongly suggesting Agent Orange as the source of the elevation.[7-10,13,16-18,20-24] We were able to find such persons from Hue and Da Nang in central Vietnam, to Ho Chi Minh City, Song Be Province, Tay Ninh Province, and, in fact, in some residents of every location sampled in the south. Levels varied, as would be expected since the 12,000,000 to 20,000,000 gallons of Agent Orange and related herbicides were sprayed by air or by ground troops in limited areas in the south and dioxin levels varied in different batches of Agent Orange. In the north of Vietnam we found very low levels of dioxins in all human tissues tested.

Measured individual TCDD levels in the south of Vietnam during the 1980s have been as high as 140 ppt in blood or adipose tissue lipid, although levels as high as 1,500 ppt were found by Baughman from 1970 samples in the milk of Vietnamese nursing mothers in the first measurements of dioxins ever in humans.[44] Figure I presents TCDD levels in human breast milk from Vietnam on a lipid basis (which has been found by us and others to be the same in blood lipid or in adipose tissue lipid). The samples with positive findings from 1970 to 1973 range from 100 to 1,500 ppt reported on a lipid basis, as is now customary. By contrast, levels of TCDD in Americans in the general population usually average 3 to 6 ppt in adipose tissue or blood lipid. In the United States general population TCDD typically provides a very small percent of the total dioxins present (< 1%), and contributes approximately 10 to 20% of the total dioxin toxicity in humans. However, in persons heavily exposed to Agent Orange, the TCDD contribution can be far higher.

To date we have sampled an estimated 4,000 Vietnamese using fat tissue, milk, blood, or autopsy samples of various organs. Initially we analyzed individual samples. Later we turned to pooled samples, combining milk or blood from up to 100 persons from a specific geographic location, prior to dioxin analysis. This was done partially because of the cost of dioxin analyses which, when conducted by qualified laboratories on a commercial basis, can range from $1,200 to $2,500 per analysis. There are also currently approximately 15 to 20 laboratories worldwide with established credentials in human tissue dioxin analysis, so capacity is limited. Pooling of specimens can also more rapidly answer the key question in exposure assessment to define where in Vietnam dioxin from Agent Orange got into humans, and what the average TCDD and other dioxin tissue levels are. This

is a key question for the approximately 2,500,000 Americans who served in Vietnam and the 17,000,000 Vietnamese who lived in the south when the Agent Orange spraying occurred between 1964 and 1970.

Figure II presents selected TCDD levels from our series of individual dioxin adipose tissue analyses from Vietnam that were taken in 1984. These illustrate the considerable variation in the levels of TCDD in human tissue from the south of Vietnam. 2,3,7,8-TCDD is abbreviated as TCDD on this and other figures in this communication.

In Figure III variations in dioxin toxicity in Vietnamese are shown as "dioxin toxic equivalents." "Dioxin toxic equivalents" (TEQ) are calculated using the currently accepted "International" toxicity factors for dioxins, and proposed toxicity factors for PCBs.[25-27] In this now widely accepted scheme which was initially developed to deal with the existence of multiple dioxin and dibenzofuran congeners in the dioxin-contaminated Binghamton State Office Building, all of the dioxins and dibenzofurans are rated as to their relative toxicity in comparison to 2,3,7,8-TCDD.[45] Dioxin and dibenzofuran congeners other than TCDD have an identical effect on human health; therefore, it is important to consider all the toxic 2,3,7,8, chlorine-substituted PCDDs and PCDFs when estimating dioxin exposure. The dioxin toxic equivalents in human blood in Figure III present the summation of all the dioxin and dibenzofuran congeners to total dioxin toxicity in Vietnamese. It is evident that even in Vietnamese living in Vietnam, there are currently different dioxin body burdens, reflecting varying intake of dioxins from Agent Orange and from industrial contamination.

Fate and distribution of TCDD from Agent Orange is illustrated in Figure IV. Silt from the Saigon river in the south of Vietnam showed high levels of TCDD while TCDD was not detected in samples from the Dong Nai river in the south of Vietnam where we sampled it, or the Red river in the north of Vietnam.[12,15]

Wildlife in Vietnam also had uptake of TCDD from Agent Orange which is illustrated in Figure V. Elevated 2,3,7,8-TCDD was found in turtle liver, muscle, gallbladder, ovaries and in snake tissue in selected areas in the south,[11,14] documenting bioavailability, which as we know from the work of Umbreit and Gallo, varies with the matrix in which TCDD is found.[46]

Vietnam offers an ideal epidemiological setting for the study of Agent Orange. Since it is where Agent Orange was sprayed, many Vietnamese were exposed during the spraying and thereafter; the Vietnamese potentially had more exposure than U.S. troops because they did not serve only one year tours of duty

that were typical for Americans. The Vietnamese lived off the economy and consumed food and water contaminated with TCDD and the Agent Orange phenoxyherbicides. TCDD serves as a marker of itself and also of the herbicides 2,4-D and 2,4,5-T, which together, constituted Agent Orange. 2,4-D by itself is apparently carcinogenic, as shown by several National Cancer Institute studies.[47,48] Although large numbers of Vietnamese in the south have elevated dioxin levels, there are also Vietnamese in the south and far more in the north with a much lower body burden of TCDD as well as other dioxins. Since Agent Orange spraying in Vietnam began in 1962 and ended in 1970, several decades have elapsed since initial exposure, which should provide sufficient time for development of some cancers associated with dioxin exposure, if they exist.

From an epidemiological perspective, having large populations of men, women and children with elevated dioxin levels, large populations with lower levels of dioxins, and a latency time of decades since initial exposure for expression of possible cancer development provide ideal study conditions. Government health agencies, medical schools and tertiary care hospitals in Vietnam are willing to cooperate with American scientists in studies dedicated to finding answers to the questions of Agent Orange health effects by means of collaborative health studies in Vietnam.

Collaborating chemists in our Vietnam work included, in alphabetical order: Michael Ball, Brian Eitzer, Peter Fürst, Christiane Fürst, Michael Gross, Ronald Hites, Anton Lis, Kees Olie, Olaf Päpke, Seppo Raisanen, J.J. Ryan, James Startin, and Christopher Wright.

MASSACHUSETTS VIETNAM VETERAN STUDY

In the Massachusetts Agent Orange Commission Agent Orange studies we used adipose tissue and blood, for congener specific dioxin and dibenzofuran measurement to determine TCDD and total dioxin-like toxicity in veterans. The laboratories of Dr. Michael Gross of the University of Nebraska, Dr. John Jacob Ryan of Health and Welfare Canada, and Dr. Christopher Rappe of the University of Umea in Sweden performed the dioxin analyses for these studies.[1-6]

A minority of the veterans selected as having potential Agent Orange exposure showed elevated TCDD in a pattern consistent with intake of Agent Orange and its dioxin contaminant when blood was obtained several decades after potential exposure. TCDD levels measured approximately 20 years after exposure

in twelve veterans from this study are presented in Figure VI. Varying levels of dioxin exposure were found in ground troops and also in the Air Force herbicide sprayers, the "Ranch Handers."

In twenty veterans we found that blood plasma and adipose TCDD measurements were very similar, when reported on a lipid basis (i.e. measuring the fat soluble dioxin congener in the lipid fraction only). This can be seen in Figure VII which presents the ratio of blood plasma to adipose tissue for the measured PCDD and PCDF congeners. We and others have found 2,3,7,8-TCDD blood and adipose levels to be quite similar, here with a 0.83 plasma to fat tissue ratio. In the higher chlorinated dioxins however, as much as a two-fold difference is noted between blood lipid and adipose lipid levels in the case of octachlorodibenzodioxin or OCDD. In reading the literature, or extrapolating between various tissues, such as fat or blood to body burden, these differences must be taken into account. Our autopsy studies found varying congener levels in different organs of the body, even when normalized and presented on a lipid basis.[49,50]

MICHIGAN VIETNAM VETERAN STUDY

The Michigan Agent Orange Project, which we are finishing at the present time, involved study of 50 Vietnam veterans who reside in Michigan.[5,6] Dioxins, dibenzofurans, and the dioxin-like coplanar PCBs, mono-ortho substituted, and di-ortho substituted PCBs, were measured in whole blood in order to determine the feasibility of using dioxin tissue measurement to identify persons with intake of Agent Orange several decades after exposure and assess relative levels of exposure. Dioxin toxic equivalents at the time of sampling were calculated and levels at the time of exposure were estimated based on assumptions concerning half-life of elimination of TCDD.[25-27] The study was also concerned with reproductive toxicity from dioxins, because of the hypothesis considered by Maureen Hatch and Zena Stein, that dioxin levels in semen might possibly contribute to male mediated reproductive effects.[51] This study is the first to have detected dioxin levels in semen.

Figure VIII shows elevated TCDD from Agent Orange in the blood of some Michigan veterans two decades or longer after exposure. Elevated TCDD above 10 ppt was found in 6 of 50 persons, including 4 Army ground troops, as shown in Figure IX; nine veterans had TCDD levels above 7 ppt. When measuring dioxin-like PCBs and all measurable PCDD/Fs, we find, as does a CDC study, that,

PCBs markedly increase dioxin toxic equivalents. Using present assumptions as to PCB dioxin-like toxicity, which may overstate actual toxicity, it is estimated that adding PCB dioxin toxicity equivalents to the dioxin and dibenzofuran dioxin toxic equivalents (TEQs) more than doubles the dioxin toxic equivalents.[27] Figure X illustrates the average contribution to dioxin toxicity of PCDDs, PCDFs, and PCBs. It shows that, for persons in the general population exposure range, using current estimates of PCB dioxin-like toxicity, PCBs contribute more to dioxin toxic equivalents than do the dioxins and dibenzofurans.

Dioxin-like toxicity of many PCB congeners may be less than that of some dioxins, but the PCBs are present in human tissue in the United States in much higher amounts than are dioxins. The levels of the dioxin-like PCB congeners found in the Michigan study appears to be almost identical to levels found in a smaller study by Patterson and Needham at the Centers for Disease Control in their general population report.[52] The Michigan Veterans had no known special exposure to PCBs, only the potential for exposure to Agent Orange and its dioxin contaminant, 2,3,7,8-TCDD. Therefore, we feel that their PCB levels are similar to levels in the general U.S. population.

We have recently been able to detect and quantitate, in a congener-specific fashion, dioxins and dibenzofurans in semen in the Michigan study. Figures XI and XII present dioxin and dibenzofuran congener specific mean values from three pooled semen analyses. The lipid level was very low, below detection, in the semen specimens, therefore these results are reported on a wet or whole weight basis, not normalized to a lipid basis as are the blood analyses. In order to have sufficient volume to conclude the studies in a timely fashion, it was necessary to use pooled semen; comparisons of blood and semen dioxin levels from the same patients are not yet available. Nevertheless, the finding of dioxins and dibenzofurans in semen for the first time does give some support to the hypothesis that such dioxin contact may provide a mechanism for possible action of these chemicals on sperm or eggs with subsequent adverse reproductive outcome. Figures XIII and XIV present, in bar graph format, the mean dioxin and dibenzofuran levels by congener groups in blood from the fifty Michigan Vietnam veterans. In Figure XIII the mean level of 2,3,7,8-TCDD is from the 44 subjects whose blood TCDD level is below 10 ppt. The dioxin blood and semen patterns are similar but the dibenzofuran patterns appear to differ in these preliminary data.

OTHER RELEVANT EXPOSURE ASSESSMENT STUDIES

Several other studies related to exposure assessment, which we and others have conducted, are relevant to Vietnam Veterans. Our own work has revealed characteristic low levels of most dioxin congeners in human tissue in less industrialized countries and much higher levels in industrialized countries. [53] Certain exceptions include the elevated dioxins from Agent Orange and the industrial sources in Vietnamese living in the south and elevated DDT and DDE levels in all Vietnamese studied. The possible exposure of Vietnam Veterans also to other toxic chemicals while in Vietnam should not be ignored in considering adverse health outcomes from Vietnam service.

We previously found that ancient frozen Eskimo tissue from Point Barrow Alaska has extremely low levels of dioxins, again suggesting a modern industrial source for most dioxins, which is consistent with our findings of elevated levels found in humans from the more industrial countries as compared to less industrial countries.[54,55] We have also noted low levels of dioxins in tissue from stillborn babies with increasingly higher levels in older persons.[56] Additionally, we have found elevated dioxin congeners up to 35 years after exposure in highly exposed workers, so the persistence of dioxins in humans is well documented.[57,58]

We previously reported, with J.J. Ryan, of Health and Welfare, Canada, varying levels of dioxin and dibenzofuran congeners in various organs from the same person. Three autopsies from the U.S. general population were reported on a whole weight and on a lipid basis, allowing comparison between adipose tissue and other organs on a congener by congener basis.[49] These same autopsies were reanalyzed for PCB congeners by Jos Mes, also of Health and Welfare, Canada.[50] We thus have the beginning of a database for moving exposure assessment from simply reporting blood or fat levels to a more accurate estimation of target organ levels. Since insufficient numbers of autopsy analyses have been performed to date to allow extrapolation from blood or fat dioxin levels to target organ of concern with a high degree of confidence, we and others usually estimate from blood or adipose lipid to body burden. This approximation needs to be replaced with actual data based on autopsies from persons with various levels of exposure.

The measurement of dioxin, dibenzofuran and dioxin-like PCB congeners in blood, performed in the laboratory of John Stanley with the assistance of Kathy Boggess at the Midwest Research Institute, Kansas City, Missouri, suggests that exposure assessment for individuals or in epidemiology studies may not be

accurate for total dioxin-like toxicity unless such complete measurements are taken. This does not mean that our estimates of where intake of dioxin took place in Vietnam based upon mapping out of dioxin levels in pooled blood in various geographical regions in Vietnam or by a computer model such as that used by the Stellmans may not be sufficient to answer some individual health-related questions or to provide the scientific basis for Vietnam veteran exposure estimates. These, in turn, will have applicability for the Veterans' Administration in determination of compensation issues. In my opinion, various approaches have merit and should be used where appropriate.

OTHER RECENT, RELEVANT HEALTH STUDIES

There are several recent studies of the health effects of dioxins or 2,4-D which suggest increased urgency in examining the health effects of exposure to Agent Orange in Vietnam, including issues of exposure assessment. In two separate National Cancer Institute studies by Dr. Sheila Hoar Zahm and colleagues, increased cancers were found in some Kansas and Nebraska farmers exposed to the herbicide 2,4-D.[47,48]

Increased cancer mortality has also been noted in at least four studies conducted respectively by Fingerhut and colleagues at CDC's National Institute on Occupational Health, by Zober, Manz, and by Saracci.[59-63] These studies support links between dioxins and cancers of various types and tissues and follow and build upon earlier studies by Hardell and colleagues.[64] The dioxin and cancer causal linkage is also supported in 19 out of 19 positive cancer studies in animals.[65]

There is also cause for concern following dioxin exposure for other than cancer health effects. Peterson and coworkers at the University of Wisconsin, in a series of elegant studies, have reported greater sensitivity to dioxins in reproduction and fetal development when compared with cancer.[66-68] Recent findings reported by Birnbaum of the EPA Human Effects Research Laboratory (HERL) also suggest that the immune system as well as the reproductive system are more sensitive to the effects of dioxins than is the cancer endpoint upon which we so often focus our attention. In addition, the Ranch Hand study and NIOSH studies of TCDD exposed veterans or workers have each independently found dose related diabetes mellitus and altered lipid metabolism, exhibited by increases in blood lipids. These latter are potentially linked to adverse

cardiovascular and cerebrovascular events.[69,70] Finally, Lucier and colleagues at the National Institute of Environmental Health Sciences report similar tissue sensitivity of humans and laboratory rats to dioxins and related chemicals.[71] Thus, humans may well be a species of intermediate sensitivity to dioxins and structural analogues, which means humans are sensitive to very small amounts of dioxins.

Central and peripheral nervous systems problems in dioxin exposed humans have been reported by Oliver et al.[72] and in our own studies of workers exposed to dioxins after a PCB transformer fire.[73] Dr. Walter Rogan of the National Institutes of Health documented cognitive and behavioral changes in children whose mothers have had PCB or dibenzofuran exposure in separate studies with PCB levels in the general population range in one study in North Carolina.[74,75] Studies by Bowman with monkeys on 2,3,7,8-TCDD and by Seegal and Schantz with PCBs show central nervous system changes which in some cases are clearly from non-dioxin-like PCBs, but in other cases may be from dioxin-like PCB's or PCB contaminants, the dibenzofurans.[76,77] These studies suggest the hypothesis that one possible consequence of dioxin exposure on the central nervous system, like that of lead, may be a decrease in IQ for children. The possible additive or synergistic effect of dioxins and lead or other neurotoxicants on cognitive or behavioral functions in children has not yet been studied but is worthy of concern.

RECOMMENDED FUTURE STUDIES

A. Environmental and Health Studies

(1) Pooled blood dioxin levels from Vietnamese living in the south of Vietnam should be used to map out geographically where dioxin from Agent Orange actually got into people, and where this did not occur. Environmental sampling may also contribute information on bioavailability and intake.

(2) Agent Orange health studies should be conducted in the south of Vietnam, and should include women and children as well as men. The results can be used to help male and female American veterans and their families. Levels of exposure were

usually higher for the Vietnamese, of whom large numbers were exposed for a longer time than were the Americans.

(3) Vietnamese immigrants to the U.S. who were potentially exposed to Agent Orange in Vietnam should be studied. This may reveal Agent Orange health effects or the lack thereof, which would be reassuring to all potentially exposed to dioxins, including U.S. Vietnam veterans.

B. Basic Scientific Exposure Assessment Studies

(1) It is not known how to interpret levels of dioxins in the blood (lipid) of cancer patients with wasting. We do not know whether levels go up, go down, or remain constant, in blood or other tissues on a whole or wet weight or lipid basis with weight loss. These questions can be answered quickly and at relatively modest cost in U.S. medical centers.

(2) Sufficient autopsy characterization of levels of dioxin, dibenzofuran and PCB Congeners are needed to allow us to extrapolate from blood fat levels to levels in target organs of concern and to determine body burden with confidence. This too, can be easily determined at a relatively modest cost.

(3) The validity of different methods of estimating exposure to Agent Orange should be tested against one another. Human tissue levels in veterans and in Vietnamese are being generated and computer modeling has been done, but the two approaches have not been compared, nor has an attempt been made to determine whether we can refine computer modeling to predict dioxin body burden.

(4) Leftover or archived 2,4-D and 2,4,5-T should be analyzed for various dioxin congeners which may have toxic effects, using modern methods of chemical analysis. Our study of Russian chemical workers exposed to 2,4,5-T found elevated dioxin and dibenzofuran congeners in their blood, in addition to 2,3,7,8-

TCDD. Before old stocks of these chemicals are destroyed, it would be useful to reanalyze samples from various manufacturers of Agent Orange.

POLICY RECOMMENDATIONS

The most important conclusion I have, based on over a decade of work on dioxins and Agent Orange in U.S. veterans, as well as persons living in Vietnam and other dioxin exposed persons in the former Soviet Union, Germany, and Japan, is that questions regarding the fate and health consequences of Agent Orange and its contaminant dioxin will be best and most rapidly be answered by intensive scientific and medical research in Vietnam, where Agent Orange was used--with complementary work in the United States. This does not mean that U.S. investigations of veterans should not also be performed, but that parallel studies in Vietnam must be performed or we may never have answers to many of the questions regarding Agent Orange Health effects. And certainly we will not have these answers in time to be of use to Vietnam veterans and their families.

Thirty five million Vietnamese men, women, and children live in the south of Vietnam where Agent Orange was sprayed. Half of them have lived there since the spraying. The Vietnamese did not have only a one year tour of duty "in country" as was the case for most of our veterans. They have had the heaviest known exposure for the longest number of years, there has been sufficient latency for Agent Orange related cancers or other illnesses to develop if they are going to develop, and, the dioxin body burden in Vietnamese varies considerably in the south of Vietnam. An ideal situation exists for epidemiology studies to find where TCDD from Agent Orange was bioavailable and entered humans and also what levels of dioxins are associated with health effects in the Vietnamese. Both questions are of critical importance to Vietnam Veterans and their families. This long after spraying, Vietnam uniquely, may well provide answers as to the health effects of Agent Orange.

There is an additional reason to study the effects of Agent Orange in Vietnam. Agent Orange was sprayed only in South Vietnam where our allies, not our enemies, lived. It seems morally and ethically right for our country to show compassion for those Vietnamese on whose behalf so many Americans, as well as Vietnamese, died or were wounded during the war. We showed such compassion for our former enemies in Japan by establishing medical and public health

studies in that country immediately after the war to study and help alleviate the health effects of the atomic bomb. It seems only right that we should show the same compassion for our former allies, and establish investigations and possibly an Institute in Vietnam to study the health consequences of Agent Orange.

Because of the kinetics of elimination of dioxins in humans, the time remaining is relatively short in which to initiate such studies. In my opinion, one of the most effective ways to answer the questions raised regarding the health consequences of Agent Orange, in a timely fashion to be of use to Vietnam veterans and our former allies living in the south of Vietnam, is to establish a scientific or public health office in the executive branch of government with authority from the White House to focus exclusively on health effects from the Vietnam War. The office could be modelled after the Special Action Office on Drug Abuse (SAODAP) established by President Nixon. To be most effective it should have its own "Tsar," or director, with direct access to White House senior staff, a talented scientific staff, experienced government administrators, senior dioxin literate scientific advisors, and a mandate to cut across governmental agencies and produce results in a finite number of years. Although federal government funding is essential, credibility will be far higher in the Vietnam veteran constituency if the research is conducted not by the government, but by medical schools and universities.

We have devoted considerable resources and energy to date on resolving the very important MIA/POW issue, which is a reasonable and humane thing to do. It is now equally important to focus on the health needs of over 2 million Vietnam veterans and their families, and to spend at least an equal amount to help the living, as we did to help the families of the missing and dead.

All Vietnam veterans who want an occupational medical evaluation, including, but not limited to, dioxin fat or blood analysis, should have this option, as a humanitarian gesture in return for their service. Probably a minority of the veterans would take advantage of such a program. The Veteran's Administration traditionally evaluates and treats veterans for wartime illness. Insurance companies will not usually pay for war-related chemical testing. However, a dioxin blood test, without medical interpretation, is as useless as any other medically ordered laboratory test without medical interpretation, and should not be performed in a vacuum without skilled medical evaluation.

If your Committee makes scientific recommendations or policy recommendations without suggesting an administrative framework which will

allow scientific problems to be resolved and make sure the answers will be used to help Vietnam Veterans, the work of the Committee will be incomplete. I cannot emphasize too strongly at this time the need for a Special Action Office as I have described to make the breakthroughs we require in our knowledge of Agent Orange environmental fate and health effects.

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FIGURE I: TCDD IN HUMAN MILK FROM VIETNAM 1970-1988

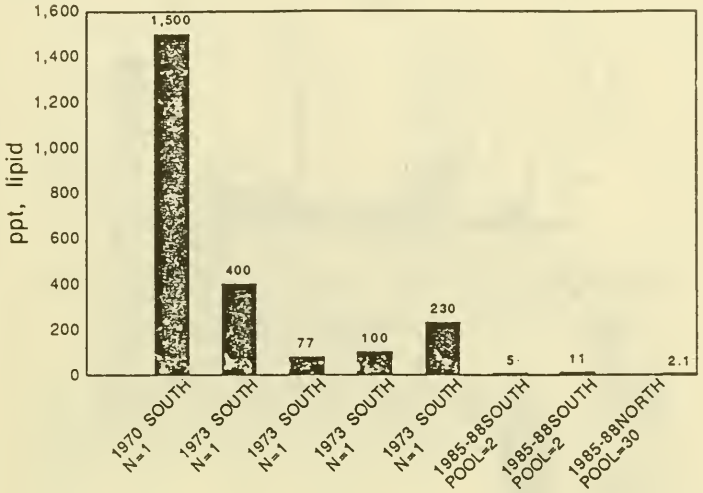

FIGURE II: TCDD IN INDIVIDUAL HUMAN ADIPOSE TISSUE VIETNAM - 1980's

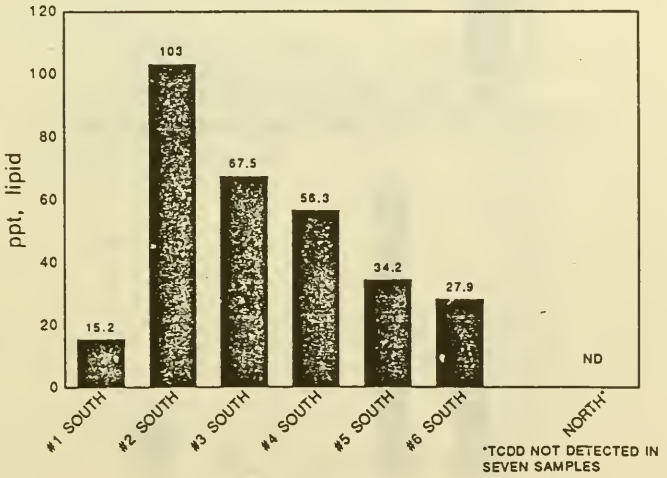

FIGURE III: DIOXIN TOXIC EQUIVALENTS IN POOLED BLOOD FROM VIETNAM, 1984-1991

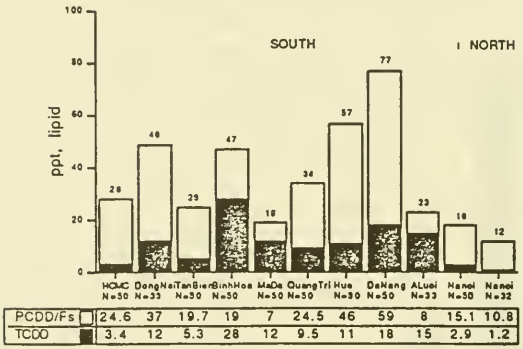

FIGURE IV: TCDD IN RIVER SILT FROM VIETNAM

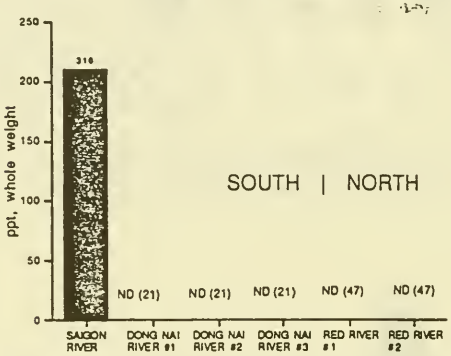

FIGURE V: TCDD IN WILDLIFE FROM SOUTHERN VIETNAM

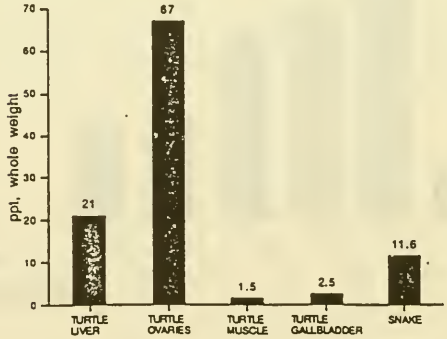

FIGURE VI: TCDD IN ADIPOSE TISSUE FROM THE MASSACHUSETTS VETERAN STUDY
(samples averaged 97% lipid)

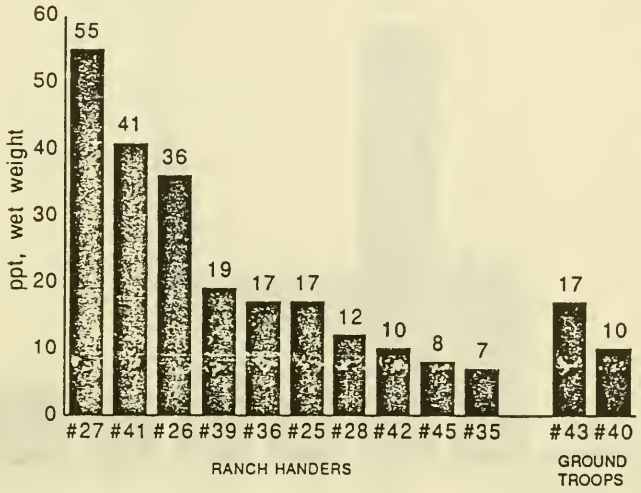

FIGURE VII: RATIO - PCDD/F CONGENER PLASMA TO ADIPOSE TISSUE (N=20)

DIOXINS	
2,3,7,8-TCDD	0.83
1,2,3,7,8-PnCDD	0.92
1,2,3,4,7,8&1,2,3,6,7,8-HxCDD	0.94
1,2,3,7,8,9-HxCDD	1.3
OCDD	2.0
DIBENZOFUANS	
2,3,7,8-TCDF	0.81
2,3,4,7,8-PnCDF	0.90
1,2,3,4,7,8-HxCDF	1.2
1,2,3,4,7,8-HxCDF	1.5
2,3,4,6,7,8-HxCDF	0.8
1,2,3,4,6,7,8-HpCDF	1.5

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FIGURE VIII: ELEVATED TCDD IN BLOOD OF MICHIGAN VETERANS COMPARED WITH MEAN OF NON-ELEVATED (ppt, lipid)

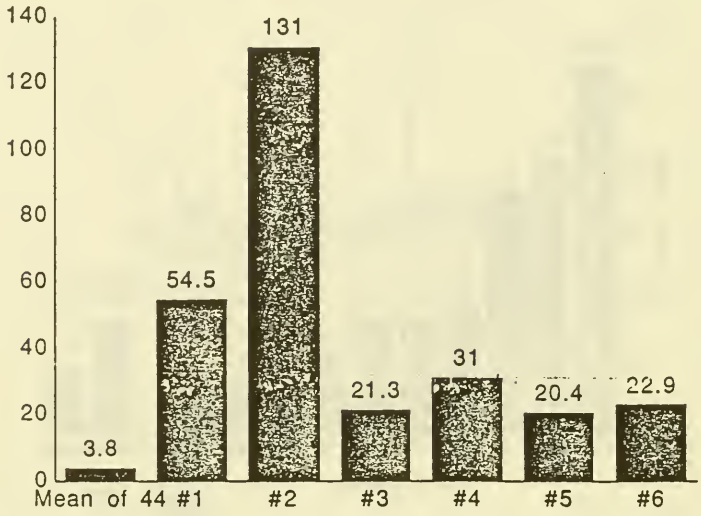


FIGURE IX: MICHIGAN VIETNAM VETERAN AGENT ORANGE STUDY

Branch of Service	Number of Veterans	Number of Veterans with TCDD above 10 ppt, lipid
ARMY	24	4
AIR FORCE	14	2
MARINES	7	
NAVY	4	
COAST GUARD	1	
Total	50	6

FIGURE XI: MEAN DIOXIN LEVELS IN COMPOSITE SEMEN SAMPLES (N = 17)

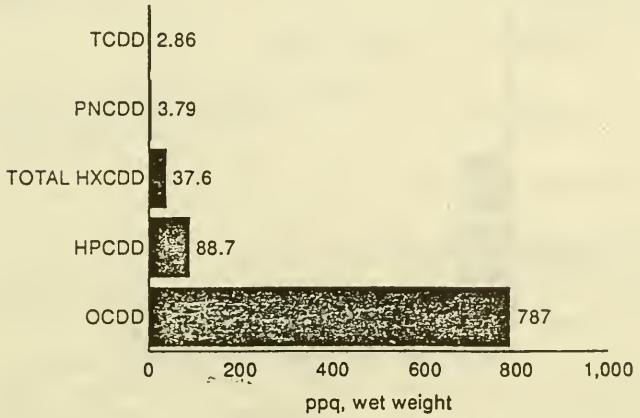


FIGURE XII: MEAN DIBENZOFURAN LEVELS IN COMPOSITE SEMEN SAMPLES (N = 17)

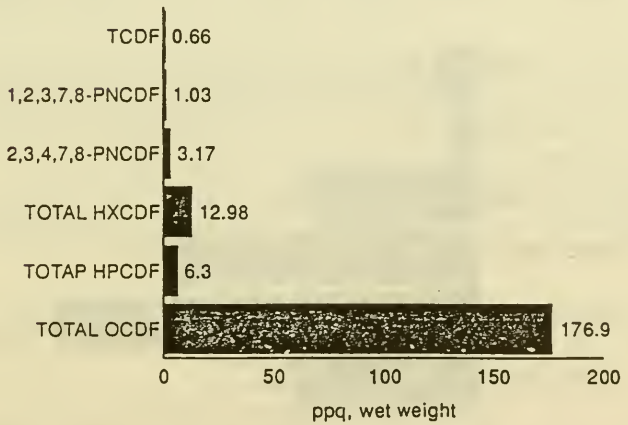
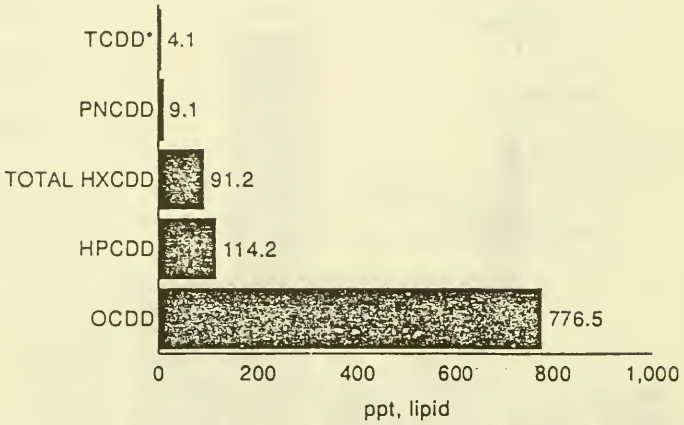
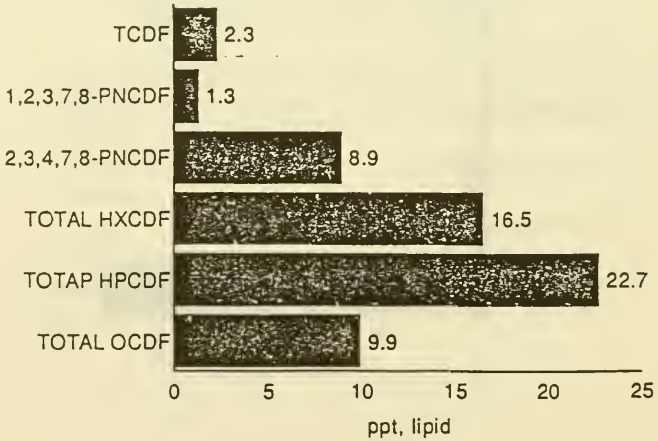


FIGURE XIII: MEAN DIOXIN BLOOD LEVELS
(N =50)



* TCDD MEAN OF 44 NON-ELEVATED

FIGURE XIV: MEAN DIBENZOFURAN BLOOD LEVELS
(N = 50)



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November 4, 1993

Senator John D. Rockefeller, IV, Chairman
Committee on Veterans' Affairs
United States Senate
Washington, DC 20510-6375

Dear Senator Rockefeller:

At the conclusion of the November 2 hearing on Agent Orange at which I appeared as a scientist-witness, the Chair requested that suggestions and recommendations for action be given to the Committee. I should like to take the opportunity to provide these in this letter, which I hope will be added to the hearing record, in addition to my other participation and written material.

Agent Orange, an unique combination of herbicides contaminated with dioxin, was sprayed in Vietnam. Therefore, we can learn about health effects of Agent Orange the most rapidly and in the most comprehensive and cost-effective fashion in Vietnam. Seventeen million Vietnamese lived in the south of Vietnam when Agent Orange was sprayed there and thirty-five million live there now. These comprise the world's largest dioxin-exposed and Agent Orange-exposed population. Men, women and children were exposed, and have lived there since the spraying. A large population with low levels of exposure, an ideal control population, is also found in Vietnam. The answers to exposure and health effects questions from Vietnam would also apply to our American Vietnam veterans, where it is hard to find high exposure, a good control population with low dioxin tissue levels, or long exposure (our veterans usually were in country for one year of exposure, not 20 to 30 years as were the Vietnamese).

The Vietnamese are organized for research and wish to work with us. My colleagues and I have conducted such research for over 10 years. We have published results establishing dioxin exposure from Agent Orange in Vietnamese living in the south, where spraying occurred.

Agent Orange and dioxin research relevant to American veterans should, for the most part, be funded and performed by scientists in American universities and medical schools. This traditional American biomedical research approach has produced a majority of Nobel prizes in the biological sciences and medicine. Small, targeted studies could be funded through NIH

or EPA grants or contracts, or a special action office could be set up with an Agent Orange czar as part of the administration to coordinate and fund such work, as was done by former President Nixon with drug abuse prevention.

The amount of funding to help the 3 million veterans potentially exposed to Agent Orange should be equal to the MIA-POW funding, as important as the latter is to help the families of the 2,200 MIA-POWs. We should not forget the needs of the living; all our Vietnam veterans deserve an equitable consideration and equitable resources to solve their problems and answer their questions. A minimum of ten million dollars a year, wisely spent among many interdisciplinary research teams, should produce answers beginning in a reasonably short time.

Mega-research projects can frequently produce very little in science for the amount of time, money and human resources spent. I believe this may have been the case with the Ranch Hand study and was the case for the CDC Agent Orange "validation" study. For answers to the questions of where exposure occurred in Vietnam and at what levels and with what health consequences, small research projects funded at a level of from $100,000 to $350,000 each per year should produce answers. These should focus on exposure assessment, cancers, reproductive problems, immune deficiencies, central and peripheral nervous system pathology, endocrine alterations, liver damage, cardiovascular disease and possibly other health effects.

The CDC dioxin laboratory is a good laboratory, but has tried to avoid, in my judgement, American dioxin problems, such as Agent Orange. Instead, CDC has focused their resources primarily on one Italian dioxin incident, interesting as it is. U.S. taxpayers' money should first be spent to address American problems. The Italian government can fund its own dioxin research, with its many excellent chemists and epidemiologists. The CDC dioxin laboratory, an existing resource staffed by salaried U.S. government employees, could be used to perform dioxin blood or tissue analyses for Vietnam Agent Orange work at lower cost.

The rice oil poisoning incidents in Japan and Taiwan, Yusho and YuCheng, respectively, with dioxins and dioxin structural analogues should be studied by American scientists because their lessons for human health almost certainly applies directly to American veterans.

Agent Orange Centers could be established at 3 to 6 American medical schools to coordinate smaller targeted research projects which should address and answer Vietnam veterans' concerns. These could provide a critical mass

of scientists, and a coordination of resources including educational resources.

Vietnam veterans should be evaluated by trained and experienced occupational medicine physicians. Dioxin blood analysis should be performed, where indicated, as part of a medical workup for Agent Orange exposure, if only to demonstrate low dioxin exposure and lead to reassurance, and such analyses should be performed at no charge by the CDC or another World Health Organization certified laboratory.

Scientific committees evaluating Agent Orange or dioxins should be composed of scientists from universities, veterans, and government scientists active in dioxin research, not policy-making administrators, whatever their previous scientific training. Future Institute of Medicine-National Academy of Sciences committees should have experts with scientific knowledge, training and experience in the dioxin field. It makes no sense to constitute a committee of distinguished obstetricians to determine what the scientific literature shows in the field of cardiology. They are both physicians and perhaps scientists, but the disciplines are different. A balanced committee of experienced scientific and medical experts is important and perhaps essential for reaching comprehensive and valid scientific conclusions.

Scientists with knowledge of dioxin health effects should be invited to come to the U.S. to discuss their findings and knowledge of the field. One cannot ask questions of a published paper, or learn of new developments. It is unreasonable to expect scientists from Japan, Taiwan and Vietnam to pay their way to come to Washington at great expense to discuss their research findings. A trip might well cost $3,000 and the monthly salary of a Vietnamese scientist is probably under $100 per month. If we wish to learn what these scientists have learned as it might help our veterans, we must invite them to come, at our expense, to discuss health consequences of dioxins and related chemicals.

Time is of the essence to evaluate Vietnam veterans' questions concerning Agent Orange and health. Although dioxins can last in humans as long as 36 years after heavy exposure, for a medium or low exposure, the chemicals may be gone from the body several decades after exposure in Vietnam. The longer we delay, the less chance of getting medically sound answers. Also, those with highest dioxin exposure are at most risk and may die sooner rate than others, making study of their cases impossible. A sense of urgency is needed in this matter.

As a Vietnam Era veteran, I hope to see renewed effort and resources from the Congress directed at effectively solving this difficult problem which has caused so much unhappiness to so many Vietnam veteran families. Thank you for your past efforts in this complex matter. And thank you for permitting me to share my scientific and medical knowledge with you. I hope to continue to serve my country now by helping to solve this medical puzzle, as I once served in the Army Medical Corps.

Sincerely yours,

Arnold Schecter

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Testimony of Ellen K. Silbergeld, Ph.D. before the Senate Committee on Veterans' Affairs: Current State of Knowledge and Research Directions

November 2, 1993

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I am pleased to respond to the invitation of the Committee to provide this testimony on the important subject of the state of the science on the health effects of Agent Orange, with particular reference to veterans of the Vietnam War. This testimony, and my oral comments, are submitted by me as an individual, at your invitation. I am senior toxicologist with the Environmental Defense Fund, and professor of epidemiology and toxicology at the University of Maryland Medical School, in Baltimore. I am also adjunct professor of health policy and management and environmental health sciences at the Johns Hopkins School of Public Health. Over the past decade, I have served on several federal advisory and expert committees that have been charged with considering aspects of the human toxicology of components of Agent Orange, particularly 2,3,7,8-tetrachlorodibenzo-p-dioxin. Among these appointments, I have been a member of three EPA scientific advisory committees on the health effects and risks of the dioxins, from 1985 through the present; I have been a member of an NRC committee on evaluating dioxin-like products of PCB fires; and I have been a member of the advisory panel on the Ranch Hand studies. I have also been actively involved in basic research on the toxicity of the dioxins, and I have published several papers in the peer-reviewed literature and presented papers on my research at international and national scientific conferences. I shall draw upon these experiences in this testimony.

My comments today concern the following topics:

1. The state of knowledge of the human health effects of Agent Orange and its constituents;

2. The quality of research conducted on Ranch Hand personnel by the Department of Defense, and its review by the National Academy of Sciences

3. Current needs for further research; and

4. Recommendations as to structures and processes for this research.

1. Current state of knowledge of the human health effects of Agent Orange and its constituents

Over the past decade, government and industry have been occupied with resolving the qualitative and quantitative nature of the health risks associated with 2,4,5-T, 2,4-D, and the dioxins. This debate has focussed narrowly upon the issue of whether these chemicals, present in empirical mixtures of herbicides contaminated by chlorinated dibenzodioxins, are carcinogenic to humans. After much contention, it is now generally concluded that much of the qualitative controversy has ended: in the opinion of most scientists, the mixture of chlorophenoxyacetic acids contaminated with 2,3,7,8-TCDD -- including 2,4,5-T -- is carcinogenic to humans. In addition, important studies of farmers and production workers exposed to the other main ingredient of Agent Orange, 2,4-D, have also been found to have elevated rates of certain cancers, in studies conducted in the United States and Scandinavia.

While epidemiologic studies cannot by themselves usually provide precise quantitative information on carcinogenic risk, basic research on mechanisms of toxicity of the dioxins now

indicates that these chemicals induce cellular responses related to carcinogenesis (receptor binding, nuclear translocation, altered transcription, interference with hormonal homeostasis) at extremely low concentrations, such that no threshold can be discerned. Moreover, based upon our current knowledge of these mechanisms at the molecular level, there is no reason to assume that a threshold exists. These are the conclusions of the EPA expert scientific advisory committee, of which I am a member; they reflect a large body of basic research conducted around the world over the past decade.

In addition, the combined body of evidence from epidemiological and experimental studies also supports the conclusion that these agents are powerful growth disregulators, as first suggested by Dr T Gasiewicz and myself in 1989. As such, it is not surprising that they disrupt growth and development and that they are particularly toxic to the developing organism, including the fetus, in several species. Epidemiological evidence on populations exposed environmentally to dioxins and dibenzofurans is consistent with these conclusions: recent studies on the Seveso and Yucheng populations have found significant disturbances in the acquisition of sexual maturity in adolescents exposed in utero or as young children. These effects also occur at extremely low doses. TCDD may also have DES-like effects on the structural development of the reproductive system in utero.

These chemicals are also toxic to the immune system. Several cell- and hormone-dependent signalling systems are disrupted by TCDD, including both T- and B-cell dependent functions. The

implications of these effects can be demonstrated by significant reductions in the ability of experimental animals to combat infection; in human populations exposed to analogous chemicals among the PCB family, there is evidence of impaired immune response as well.

The skin and liver were among the first target organs identified in early occupational studies of workers exposed to these compounds. Chloracne, a systemic intoxication of basal cells of the epidermis, is a relatively high-dose response that can persist for decades, and possibly recur when body stores of TCDD are mobilized, as we have recently published in a case study. Liver toxicity includes pathophysiologic changes in the biosynthesis of heme (porphyrinopathy), alterations in hepatic lipid metabolism, and other damage.

2. **Agent Orange Research**

Much of the data cited above is <u>not</u> drawn from studies conducted on US personnel exposed to Agent Orange. This is because in many respects the Agent Orange studies are among the weakest in the literature, and controversies over exposure assessment continue to confound their interpretation. Another reason for their weakness has been the continued efforts of sponsoring agencies of the US government to obscure and deny the import of their findings. I shall not discuss the issue of exposure assessment in this testimony, except to note that it is generally good epidemiologic practice to employ as much information as possible in evaluating past exposures. Errors in exposure assessment bias results towards the null hypothesis, that is, the failure to find an effect when

one actually exists. The Agent Orange studies are also limited because they were undertaken after long delay from the point of maximal exposure, and because the population is relatively unique, consisting of young men.

The interpretations made by government officials of the Agent Orange, Vietnam-era, and Ranch Hand studies have often raised questions as to their congruence with the actual data in the studies. Too often -- as in the Vietnam era studies of birth defects and reproductive outcomes conducted by CDC -- apparently significant associations between exposure and adverse outcome were dismissed as statistical flukes or biologically implausible. The statistical dismissal cannot be invoked without good reason; the biological reasoning is more often than not based on lack of information rather than upon good information that excludes a relationship. An example of the latter critique is the early dismissal by government of the findings of increased risks of diabetes in the Ranch Hand cohort. Despite the comments of government, there is in fact a biological rationale to expect such an association: in experimental animals, TCDD disrupts hepatic lipid metabolism, resulting in increased levels of circulating lipids (hyperlipidemia); TCDD also affects insulin and glucocorticoid receptor signalling at the cellular level, effects also consistent with disruptions in glucose metabolism.

There has also been a tendency in the evaluation of Ranch Hand data to dismiss significant findings as clinically unimportant. For instance, measured decreases in the male sex hormone testosterone were discounted as being insufficient to affect

fertility. However, decreased testosterone can have consequences other than infertility: alterations in behavior and other hormone-dependent functions can occur long before fertility is measurably impaired. Similarly, measured changes in immunologic parameters have been considered unimportant; however, considering how little we know of the implications of altered immune function, this seems a cavalier response to potentially important data.

The review of Ranch Hand and Vietnam era studies conducted by the National Academy of Sciences has undoubtedly improved the quality of study design and provided additional perspective on interpretation of results to date. However, the NAS has inexplicably adopted a strategy of involving admitted nonexperts in this review process. Apparently fearful of the controversial nature of this topic, the NAS has made it a policy to avoid consulting many of the most informed scientists in the county in this advisory process. I find this decision at variance with the strategy adopted by the NAS and NRC in dealing with other controversial issues: appointing persons with a range of views and potential biases, in order to "balance" the committee's perspective without limiting its access to real expertise.

The most recent IOM review panel, which produced the report **Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam**, made important contributions to the process of understanding the nature and significant of Agent Orange for the health of Vietnam veterans. However, their inexperience with the field caused them to make some critical errors of judgment in their review, in my opinion. First, they excluded the large body of

complementary experimental evidence on these compounds, despite the clear utility of relying upon such information in evaluating epidemiologic studies (see A B Hill, A Evans, and M Susser for such recommendations). Second, they did not consult the body of relevant epidemiologic studies related to human exposures to related compounds, such as the PCBs and the dibenzofurans. There are important omissions in the studies reviewed: for instance, with regard to epidemiological studies of pulp and paper mill workers, no reference was made to the work of Milham and colleagues in Washington; no discussion was made of the increased rates of liver cancer reported in the Yusho (dibenzofurn) cohort in Japan. Methodological concerns have been raised about the Monsanto Nitro studies; these were not discussed. The brief treatment of experimental research is incomplete and uninformed. Repeatedly, the IOM report stresses that dioxin (TCDD) is not genotoxic (DNA damaging), yet at no point is the important fact noted that TCDD is a complete carcinogen, that is, an agent capable of increasing rates of tumors in rodents without any other treatment. These decisions place this committee in a minority; all the EPA committees on which I have served have included a thorough examination of the relevant experimental literature and the PCB/dibenzofuran studies.

Moreover, the IOM report adopts a curious strategy of embedding its evaluations of the potential associations between Agent Orange exposure and increased risks of cancer in a discussion of the overall prevalence of site-specific cancers, and the known causes for these cancers. The implications of this strategy are

unclear, although the result is obvious: whatever increases in risk that are associated with military service exposure to Agent Orange, these are relatively insignificant in the context of other known causes of cancer. This discussion neglects the real possibility that dioxin can act as a promoter in increasing cancer risk and as such, interact with other carcinogens, including viruses, to increase cancer risk. In the discussion of associations between Agent Orange exposure and reproductive outcomes, the important issue of hormonal function is omitted, and the discussion focusses only on male-mediated birth defects, low birth weight, infertility, and spermatotoxicity.

In conclusion, this document cannot be considered to represent a thorough and comprehensive review of all the available data published at the time the committee concluded its work.

3. Current Needs for Research on Agent Orange

As noted above, scientific consensus is converging upon the qualitative identification of TCDD, in phenoxyacetic acid mixtures and precursors, as a human carcinogen, developmental toxicant, and immunotoxin (in addition to its longstanding identification as a dermatotoxic agent and a hepatotoxin). Further epidemiological research, on the Vietnam cohort or others, is unlikely to improve this qualitative knowledge of hazard.

Given the very great expense of epidemiological research, particularly prospective longitudinal studies such as the Agent Orange research program, it is important to identify the most important needs for epidemiologic research on Agent Orange. In

some cases, our knowledge of the hazards of TCDD and related compounds may be best advanced by experimental research, on mechanisms of toxicity, and by study of cohorts that include other subjects at potentially increased risk, such as fetuses and young children. The following are listed as priorities for further research on the Vietnam veteran cohorts exposed to Agent Orange:

1. understanding the long term sequelae of exposures, particularly as the reproductive and immune system approach senescence

2. understanding the potential neurologic and neuroendocrinologic toxicity of Agent Orange and its constitutents

3. evaluating the health risks of Agent Orange for women exposed during the Vietnam era

4. refining exposure assessment through the development of sensitive biomarkers beyond tissue measurements of TCDD.

5. case control studies on veterans through the VA hospital system to collect surveillance information on incidence of health effects associated with Agent Orange.

The research recommendations by the IOM Committee embody many of these recommendations, as well as the comments in the next section as to structure and process. I strongly support the recommendations calling for refining our understanding of exposure in order to identify those veterans with relatively high exposures, as well as for developing biomarkers that move us along the process from internal dose to early cellular response. However, it must be kept in mind that our knowledge of toxicokinetics is relatively limited, so that exposure assessments and reassessments carried out

in 1993 have a tenuous relationship to back-predicting actual exposures several decades earlier.

I also support the IOM committee's recommendation to evaluate other cohorts from the Vietnam era. In addition to Ranch Hand, an evaluation of cohorts of women who served in Vietnam, forces from Australia, and the Vietnamese people, should be considered for study. The work of NIOSH and ATSDR is establishing registries of persons exposed to herbicides and TCDD provides a useful model for emulation.

5. **Structures and Processes for Conducting Agent Orange Research**

Research should not be conducted or reviewed exclusively by parties who stand to lose by positive or negative results. A continuing problem with the review process of the Agent Orange studies, including the advisory committee on the Ranch Hand studies, is the rather small circle of experts who seem to serve on all these committees (apart from the IOM panel). It is difficult to imagine how the same people who provided recommendations on study decision can be expected to provide independent evaluations of results. This problem of the closed world of scientific experts is common to much of the federal scientific advisory process, and Congress would do well to assess the extent to which agencies rely upon redundant sources of expert input, on their own advisory committees and through the NAS.

The Defense Department is not an appropriate venue for conducting research on Agent Orange. Ideally, the CDC could provide the role of research direction and implementation; however, over the past decade, leadership at CDC has identified itself too

strongly with one position in the controversy. This is not to say that government cannot conduct excellent epidemiologic research on controversial topics: the NIOSH dioxin registry studies are widely regarded as among the best epidemiologic studies ever conducted on the effects of toxic chemicals on human health. Perhaps the Agent Orange studies should be handed over to Dr M Fingerhut and her colleagues at NIOSH. Possibly the VA, under its new leadership, could be entrusted with some studies, such as the case:control studies recommended above.

If government is to conduct these studies, a strong advisory structure must be constituted and empowered to provide binding recommendations as to both study design and data analysis. In my experience, however, most advisory committees do not provide detailed oversight and only interact in a cursory way to approve the actions of government.

Alternatively, the government should look to extramural sources to conduct and review ongoing studies on Agent Orange. The extramural, academic research community contains abundant resources in epidemiological expertise and data management to handle large, complex studies. The Women's Health Initiative, a long term, prospective research project funded by NIH and carried out by several leading biomedical research institutions around the country, may provide a model for such multi-institutional academic research management. Not only are the participating institutions responsible for conducting the component studies, they are also primarily responsible for research design. The Agent Orange studies clearly need a new look at study objectives, basic

hypotheses, and research design. It is unlikely that this new look will come from the same entrenched parties within government and on advisory committees who have been responsible for the studies to date.

It has taken this country nearly two decades to reach closure on Agent Orange and the dioxins. Despite an extraordinarily rich database of both human and experimental research on the toxicology of these chemicals, administrations from President Nixon onward have been unable to enunciate coherent, scientifically based policies to acknowledge the damage caused by these chemicals to human health and the environment. This history represents one of the sorriest mixtures of science and politics, and for too long the politics of Agent Orange have dominated and obscured the science. The Agent Orange studies conducted by government have unfortunately been contaminated by this failure to keep politics out of science. Government's stake in exonerating Agent Orange was too obvious, and repeated denials of the findings of its own studies have done much to impair the credibility of government health research.

To most observers, it is clear that if Agent Orange had not been used in the Vietnam War, this country would probably have been able to reach consensus on the adverse effects of dioxin and related compounds. For too long government has feared the costs of acknowledging the truth about dioxin. It is time to transcend the political legacy of Agent Orange and to develop sound and just policies based upon the science. Further research on Agent Orange must be based upon a new pact of trust between government and scientists, between scientists and veterans.

Statement of

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United States Senate

Committee on Veteran Affairs

November 2, 1993

We are pleased to have the opportunity to address this Committee on Veteran Affairs of the United States Senate on the issue of Agent Orange and its possible effects on the health of American veterans. The testimony that I am presenting on my behalf and on the behalf of Dr. Steven D. Stellman is based on our fifteen years of experience studying the health of Vietnam veterans in relation to military use of this herbicide. During that time we have acquired a great deal of practical knowledge on this subject through many different routes. First, we have conducted studies on three different veterans' organizations, including members of the American Legion, and have reported our findings in the scientific literature; secondly, we are engaged in collaborative studies in Vietnam itself with the International Agency for Research on Cancer; and finally, for the better part of a decade we have served as Exposure Consultants to the Agent Orange Veterans Payment Program established by the U.S. Eastern District Court as part of the settlement of the toxic tort suit filed by veterans against the manufacturers of Agent Orange.

In addition to our experience in the area of Vietnam veterans' health, I have other extensive experience in public health. I am a past Guggenheim Fellow and am currently serving at the editor of the 4th Edition of the ILO Encyclopedia of Occupational Health and Safety. I have been the recipient of a five year National Cancer Institute Preventive Oncology Academic Award. I am the editor of the academic quarterly journal *Women and Health*.

Dr. Steven Stellman has also had a career in public health. He is currently Acting Chief of the Division of Epidemiology of the American Health Foundation in New York. He previously served as Assistant Commissioner of Health for Biostatistics and Epidemiologic Research for the City of New York, and was formerly Assistant Vice President for Epidemiology for the American Cancer Society. He has served on the faculty of a number of medical schools, and recently completed a National Institutes of Health Fogarty Senior International Fellowship.

We have followed the proceedings of the Institute of Medicine's Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, and have, at their request, presented our findings at an expert panel and in writing. We carefully reviewed their findings and recommendations as presented in their recently published report "Veterans and Agent

Orange: Health Effects of Herbicides Used in Vietnam." We have reviewed the DVA Agent Orange Task Force Report as well, and wish to take this opportunity to present our own synthesis and recommendations for future research, as requested by this Committee.

Recommendation: Avoid the mega-science trap. Develop a program whereby several smaller-scale, focused research projects can be undertaken.

It is now more than twenty years after the last drop of Agent Orange was sprayed in Vietnam. Yet, despite tens of millions of dollars spent on Federal research projects, our knowledge of its health effects has been advanced very little, and even the major efforts of the Institute of Medicine Committee have not resulted in a definitive statement of established health effects but rather in a broad indictment based mostly on circumstantial evidence, with recommendations for future research to fill in the missing details. One of our most important goals in presenting this testimony is to help this Senate Committee understand where this massive research effort failed, and how to avoid repeating the failure in the future.

Two reasons have been given for the failure to pin down the health effects of Agent Orange after all these years, one political and the other scientific. As you know, a House Subcommittee chaired by the late Congressman Ted Weiss (D-NY) concluded in 1990 that the CDC veteran studies were tainted by White House interference. As scientists, however, we are better equipped to comment on that study's scientific problems.

We believe that the CDC study and the Air Force Ranch Hand study were both afflicted with what we'll call the "mega-science" disease. That is, each study in its own way attempted to do it all: to study all possible health effects in relation to all possible exposures. In doing so both broke the most basic rules of epidemiology.

Epidemiology, which is the study of disease in human populations, is far from an exact science. In laboratory science one can manipulate chemical exposures of rats or guinea pigs and make minute observations of the illnesses that develop. Environmental epidemiology is not like this; the exposures that occur in the real world are rarely measured accurately if at all. It is more likely that interest in such exposures arises too late for measurement, as happened with Agent Orange.

In this situation, the best scientific strategy requires careful and repeated studies based on biologically plausible hypotheses. Because data on exposure must be reconstructed from records and, perhaps, from biochemical measurements of trace chemicals still stored in the bodies of veterans, they are far from perfect, and the uncertainty in deciding who was exposed and how much exposure there was greatly complicates the choice even of who should be in a study. As a result of this uncertainty, only in the rarest of circumstances can an epidemiologic study be

constructed that is free of flaws, and even the best epidemiologists expect their studies to be somewhat flawed. To cope with these basic scientific problems, epidemiologists have long agreed that their optimum strategy for elucidating important relationships between exposures and health effects is for many different researchers to poke at the problem in a variety of ways, using various designs. No single epidemiologic study can be called "definitive." To the contrary, experience has shown repeatedly that consensus is achieved only gradually, as each new study adds its own unique perspective to a complex problem.

That is why, for instance, at an American Health Foundation workshop last week no fewer than six independent research groups presented mixed findings on the role of aspirin in colon cancer, agreeing overall on the existence of a general protective effect, but disagreeing as to dosage, timing, side effects, and, most importantly, on what advice to give to healthy people who wish to prevent this disease. These researchers were well aware that the path of epidemiological research is strewn with discarded data arising from studies that, simply put, had grandiose aims of answering all questions in a single study.

In contrast to this usual pattern of cautious consensus, one of the least successful approaches to the study of complex environmental health problems is the "mega-science" method which attempts to investigate, shotgun-like, every conceivable question at once. Regrettably, Vietnam veterans in particular seem to have been plagued by this approach in which an attempt was made to design extraordinarily large and expensive studies to answer all questions for all time. This was the approach taken in the two largest government-run studies: the Air Force Ranch Hand Study and the CDC Vietnam Experience Study.

There are several fundamental flaws to this approach. First, it forces the researchers to look simultaneously at many unrelated health problems using a single one-size-fits-all design protocol. Since many health effects are best studied with different designs, in a mega-study few effects will be viewed with the most appropriate one. This wastes the time of the study subjects as well as of the researcher. Secondly, this approach forfeits at the outset one of the scientist's strongest tools: the ability to learn from experience or to correct mistakes, because it assumes serious mistakes won't be made. And finally, from the fiscal point of view, by putting all one's funding eggs into a single research basket, so to speak, the investigator runs the epidemiologist's two most serious risks: that of failing to observe important health effects, and that of seeming to observe effects which are really artifacts or the results of statistical flukes. The many-investigator/many-study approach is, in fact, the best protection against making these costly errors.

In conclusion, we recommend to this Senate Committee that when it begins to deliberate alternative funding strategies for new Agent Orange research, it specifically avoid the "mega-science" approach in favor of one which encourages many qualified researchers to pursue more modest studies that focus on narrower ranges of health problems. In this traditional approach we see the best chance for success.

Recommendation: Specialized sub-group studies are needed

We strongly agree with the Institute of Medicine's recommendation that studies of special groups be carried out, on the principle that any health effects of Agent Orange or other toxic chemicals should be most easily identified in the most highly exposed individuals. The Army Chemical Corps has been mentioned, and there are other "special groups" which should be identified and followed. For example, certain engineering units have been identified as having particularly great opportunity for exposure. Or, since it has already been reported by the National Cancer Institute that guard dogs serving in Vietnam suffered from excess testicular cancer, it appears to make good scientific sense to carry out a study of the troops in the scout dog unit, provided that sufficient numbers are available to make the study statistically reliable.

The original design of the CDC cohort study was to identify combat battalions that had been exposed to different levels of Agent Orange, and follow them forward in time. This basic idea, which was abandoned by the CDC, was in fact a sound one which deserves to be rejuvenated and carried out. It is not necessary to begin at square one. Much data already exist which would facilitate identification of such battalions.

Another group which has received scant attention is women veterans, mainly nurses, who staffed field hospitals and other units that were close to Agent Orange spraying. These women shared many of the same experiences and exposures as men in combat. They are a logical specialized sub-group to be studied for a variety of health outcomes.

The identification of such groups, while not a trivial matter, can be done in a systematic way utilizing data resources such as those we have developed for the Eastern District Court's Agent Orange Veterans Payment Program.

Recommendation: Require the establishment of external advisory panels for any research or database compilation undertaken

Epidemiology is not an exact science. Most often epidemiologists do not design an experiment but try to construct reasonable hypotheses in order to analyze a "natural experiment" that has already occurred. From basic observations, sometimes years after the events, the epidemiologist tries to draw conclusions about possible cause-and-effect relationships.

To do so, epidemiologists must have a clear understanding of the nature of the exposures, of biologically plausible effects that could be expected to result from those exposures, and of

many other factors which might confuse or "confound" the hypothesized relationships. In simpler language, an epidemiologist must exert some good common sense about what actually occurred, what could happen and what other factors could interfere with the "experiment."

The history of Agent Orange research is replete with examples of how common sense has not been applied to the problem. For example, despite repeated urging, both formal and informal, by those who knew better, millions of dollars have been spent by the CDC on research studying groups restricted to men with the shortest tours of duty in Vietnam, rather than the longest, often in units with little or no potential herbicide exposures. As a result, these dollars have purchased extensive data on men with minimal exposures, data which contributes very little to understanding the health issues, while most research questions remain unanswered.

Or consider that more millions have been spent studying a rather small and possibly incomplete cohort of Air Force pilots who conducted their spraying missions from sealed cockpits, rather than mechanics and spray handlers not so protected. The original cohort was not derived from official military records but from a volunteer association not representing the entire group at risk. In these Ranch Hand studies exposure was incomprehensibly "quantified" as the total amount of herbicide sprayed each year divided by the total number of men who served in any particular job category.

Moreover, most of the analyses in these studies have failed to take into account the single most serious health hazard of the war: combat. We and many other researchers have repeatedly found that combat exposure is a critical variable to be controlled in studies of veterans' health.

Individual epidemiologists have long recognized their own shortcomings in dealing with complex exposures and multi-faceted health outcomes, and have come to accept a multi-disciplinary team approach to their studies, coupled with external advisory reviewers. The purpose of such review groups is to try to prevent obvious as well as subtle mistakes. This goal can only be met if the review panel has members whose expertise covers many disciplines. But the mere existence of a review committee does not guarantee the scientific integrity of a study: the committee must be independent and impartial. These conditions were not met for either the CDC or Air Force studies. The CDC study oversight was controlled by a White House political organ, and to this day the Ranch Hand advisory group is inbred and secretive.

It is not the purpose of this hearing to determine how or why these studies were designed as they were, but rather to make the specific recommendation on how to avoid this in the future. We specifically recommend that any Agent Orange research funded by the U.S. government require the participation of an advisory panel comprising, among others, knowledgeable veterans or their representatives and people with appropriate practical technical background on the actual conduct of the Vietnam war and its military operations. These panels must not be token bodies, but their members be fully apprised of the goals of the proposed study and be given the opportunity to review and comment on all phases, from initial design to construction of the cohort, definition of exposure, execution, and statistical analysis.

One lesson we have learned from carrying out a wide range of studies involving many populations is that the input of the "community" at risk and the experts that service that community is invaluable in the construction of meaningful study designs, survey questionnaires and so on. The Congress could be guided in this recommendation by consulting with the National Institutes of Health which, in programs such as the National Cancer Institute's Cancer Control Programs has routinely required that such advisory panels be assembled.

Recommendation: Means should be provided whereby the extensive databases available for assembling and validation of the historical reconstruction of exposure opportunity can be undertaken.

Through our work with the Agent Orange Veterans Payment Program and with The American Legion we have been fortunate to have had access to data on troop movements and locations previously available only to the U.S. government. We have also had significant opportunity to work with the computerized databases available on the use of herbicides during the Vietnam war. We have previously described these databases in some detail in the appended report, which we originally prepared at the request of the Institute of Medicine. The tables in the IOM report lay out the rich array of databases available for reconstructing the likelihood of exposures among the troops.

It is extremely important that the Committee understand that an epidemiology study is only as good as its exposure measure. Again, the history of Agent Orange research is replete with studies where preposterous exposure measures have been used. We have already cited the Ranch Hand exposure measure which utilized the total gallonage dropped in Vietnam in any one year divided by the total number of men in any job classification in all of Vietnam as the "exposure" of each man in that job classification. Other inadequate measures are Corps of service in Vietnam and military occupational specialty (MOS). We discuss these methods in some detail in our appended report.

In contrast to such data measures are the large amounts of data which are available and have been extracted from actual military records. Two facts about these data are especially worth noting. First, these data were assembled entirely at taxpayers' expense, which was considerable. Secondly, their existence seems to have been a well-kept secret, and would have been buried after the CDC abandoned its Agent Orange studies had the Federal Court not obtained them through Freedom of Information Act requests. In particular, they are not well known to the very research community that will need them to do the studies we are recommending. Therefore, we hope this Committee will take steps to disseminate the fact of the existence of the data, as well as the data itself.

While none of these databases is perfect nor 100% complete, it is important that this panel realize their potential value for epidemiological studies, especially in comparison to the often much more limited data available for answering other important environmental exposure questions. Before this potential can be realized, however, the Government will have to make an investment in developing the data further. Much of these data were assembled by us for a series of specific purposes which, in general, were not related to research but rather to meet specific criteria for exposure eligibility set forth by the Court in the Agent Orange Veterans Payment Program. In our report to the IOM we concluded that:

> ...it is possible, in principle, to reconstruct the herbicide exposure opportunities of hundreds of thousands of veterans. Our principal scientific concern has to do with the accuracy of such assignments, and questions of direction and degree of misclassification which must be adequately resolved before quantitative exposure assessment methods can be routinely applied in epidemiologic studies.
>
> Before these methods can be used with complete confidence for research, further studies should be conducted that examine the limits of the methodology. In particular, sensitivity analyses of the extent to which the relative exposure rankings for individual veterans are altered by changing the assumptions used in constructing the exposures for their military units. For example, one could hypothesize specific "error" in the recorded locations of troops and/or of spraying and determine at which point such "errors" would lead to the reclassification of a veteran's exposure group. This error band could be added to the database and included in the error estimates of future studies. Some units might be eliminated if they were found to be particularly sensitive to such misclassification. On the other hand, units with "gaps" might satisfactorily be included because imputation of locations might be found to introduce no reasonable likelihood of misclassification. Thus for companies and battalions where gaps exist for a portion of their stay in Vietnam, it may be possible to identify additional significant time periods where there are no gaps whatever, covering large numbers of troops. It is quite likely that satisfactory exposure data could thus become available for many units previously rejected by the CDC through inappropriate selection criteria.
>
> We have already taken some steps in this direction within the database that we developed for the AOVPP. Our experience with handling of the records of tens of thousands of veterans has further given us confidence that, when our exposure evaluation method is used, the likelihood of a veteran's being switched from "low/no" exposure to "high" is rather remote.
>
> Finally, it should be recognized as a matter of principle that it is not necessary to know with infinitesimal precision the location of every single

> soldier in Vietnam in order perform a study which meets prevailing standards of current epidemiological practice. There are tens of thousands of potential study subjects available and controls can be located with ease since a greater number of Vietnam era veterans did not serve in the war theater than the number who did...
>
> The opportunity for scientifically sound epidemiological and clinical research is great and the underlying support system of military records provides a solid foundation for the research effort[1].

In view of the above, we concur with the recommendation of the IOM Panel that historical exposure reconstruction methods be further developed in order that they may be applied to future Agent Orange health studies.

Summary recommendation on Ranch Hand

The IOM Panel gave the Air Force Ranch Hand Study mixed reviews. It generally praised the effort but faulted specifics of study analysis.

Our recommendation for the future of Ranch Hand is based strictly on priorities: we believe the case has never been adequately made that the vast sums invested in studying this cohort are justified by their level of exposure. It is not at all clear that the men at greatest risk at the Air Force bases or in Operation Ranch Hand itself have been identified. Furthermore, there are troubling aspects of the study design, including assembly of the cohort itself, selection of the controls, and assignment of exposure which have never been adequately defended.

Thus, while we would not assign a high priority to continuation of the entire study, we think a salvage operation is in order. Specifically, we make the following recommendations. (1) The study in its present form should be shut down and future hands-on medical evaluations should be permanently canceled. (2) The data collected so far should be fully documented and released (without individual identifiers) through the National Technical Information Service as public use data sets. (3) Funds should be set aside for re-analysis of the data, and made available to researchers either through a secondary analysis program such as the competitive R-03 type grants of the National Institutes of Health or via Request for Applications. A standing external review committee should be assemble to oversee all three steps, including review of proposals and recommendation for awarding of grants. Methods of follow-up which guarantee confidentiality should be developed for scientifically sound proposals.

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[1] Stellman JM, Stellman SD. "An Appraisal of Military Records Available for Research on the Health Effects of Herbicides Used During the Vietnam War." A Report to the Institute of Medicine, February 4, 1993.

Recommendation: Do <u>not</u> construct registry of all Vietnam veterans

Recommendations have been made by the Institute of Medicine and the Veterans Administration Agent Orange Panel that the huge project of identifying and marking the military records of all Vietnam veterans be undertaken. We strongly disagree with this recommendation.

Through our work with the Agent Orange Veterans Payment Program we have had extensive experience in obtaining and working with more than 60,000 individual military records. We would like to inform this Committee that obtaining and indexing these records will be a long and burdensome task, for which we cannot see any scientific justification. Please note that it has not been obstructionism or incompetence by any branch of the government that has caused these burdens. It is an extremely arduous and time-consuming task, one which for many years has occupied a full-time staff that once number nearly 75 persons.

The index will largely be one of unexposed people. Most soldiers served in Vietnam during times and in areas that were not sprayed. A very large number are classified as Vietnam veterans and received medals for their service but, in fact, were offshore in the Navy, for example, with little opportunity for exposure.

We fear very much that if this registry is undertaken it will divert scarce funds that are better invested in other research efforts and will also delay the inception of these efforts since it will be years before the registry could be complete. Furthermore, unless vital information on the personal military histories of the "identified" soldiers is obtained, any research project undertaken would inevitably have to set about re-retrieving and abstracting the indexed files, thereby duplicating much of the initial identification work. We simply do not see the utility of the IOM recommendation.

Recommendation: Rather than creating a new and unnecessary registry of all veterans, provide the means for the development of a uniform system for identification of Vietnam veterans and uniform way of having access to records; Assure that all gathered records would be available to researchers, provided that confidentiality is guaranteed.

It is clear that individual military records are essential for establishing exposures among individuals. But rather than set about yet another Vietnam veteran "mega-project" of registering the entire military population of the Vietnam era, develop a mechanism by which a corps of experienced searchers available to researchers on a fee-for-service basis. Thus, any research project requiring records would not have to "discover" the methods by which to obtain them. The National Personnel Records Center in St. Louis and similar agencies would be in a position to cope with these new requests and research could proceed with relatively few impediments and would, given our past experience, be helpful in developing the search team.

In order to avoid repetitive work and to work toward achieving the goal of identifying those people with service in Vietnam, the records gathered under this program should be collected in a uniform manner, possibly into a separate data bank (with adequate protections for personal privacy). This data bank could contain uniform information abstracted from the military records that could be of use in future studies. As new records are requested this data bank could be consulted first in order to avoid unnecessary repetition of abstraction or collection work.

Recommendation: We endorse the Institute of Medicine conclusion that research must be independent.

The United States of America is well-equipped and well-experienced in the conduct of scientific research -- indeed, our scientific expertise and our mechanisms for reviewing and funding science are unrivaled in the world. We strongly urge this Committee to use the mechanisms already available in the National Institutes of Health for future research on Vietnam Veterans' health. The Division of Research Grants could develop the review committees, requests for proposals, funding mechanisms and so on which so that we can systematically attack the problem at hand. We strongly urge that this task be given to the NIH and not to agencies that are charged with the duties of providing benefits or otherwise servicing veterans' needs. On the other hand, we see no reason why such agencies should be arbitrarily excluded from participating in research on Vietnam veterans health. We suggest that the possibility be opened that governmental groups may submit proposals for funded research through the same channels as independent researchers, as researchers within the Department of Veterans Affairs have done for many years. If this is to occur, we would, of course, also strongly urge that such government groups be subject to external review and external advisory panel requirements.

We thank this Committee for the opportunity to present our views on the future of Agent Orange Research.

A Report to the Institute of Medicine
National Academy of Sciences

An Appraisal of Military Records Available for Research on the Health Effects of Herbicides Used During the Vietnam War

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Introduction

Every war is accompanied by a set of records that describe the troops, their deployment, their successes and failures, their health and well-being and the relationship of their efforts to the overall conduct of the military action. Military action is almost never random and there is a complex and intricately defined military structure of command in each of the branches of the military forces. Much of this structure is the same throughout the world and is based on centuries-old human experience of war-making. The United States military is no exception.

The military is imbued with a deep sense of history. Each battalion, for example, has an extremely well-documented record of its "existence." Units are anthropomorphized: they are "raised" for battles and "serve" in areas. Most units do not go out of existence at the conclusion of a war: some of the battalions which served in Vietnam date from the American Revolution and Civil War. They may be "retired," and can be "re-raised." Units bear insignias, nicknames and badges. Former soldiers can join any of hundreds of organizations that are devoted to preserving the histories and social bonds for specific military units, with annual reunions and periodical newsletters.

In contrast, the men and women who served in the unit in a sense lose their human descriptors. A soldier is called a rifle or otherwise labelled by the equipment or function he uses or carries out.

In this culture, the maintenance of accurate records is an essential and integral part of the workings of any military. It is a mistake for civilians to underestimate the importance that the military attaches to records keeping, nor the great skill in records management which they bring to the task. .Records managers achieve high rank in the military. The data described here were managed by a retired lieutenant-colonel, for example.

Further, the typical civilian picture of war and of the military focuses on combat, on troops on patrol, of soldiers in trenches and bombers. Civilians (and scientists) may not realize that as many as 80% of the soldiers on duty in a war zone never see combat. The support troops are, in turn, supported by a still larger contingent of support personnel and facilities in non-combat zones and in the Pentagon. A portion of this support effort is devoted to development, maintenance, filing and retrieval of military records.

This paper is presented in two parts. Part I describes the extensive military data available on the use of herbicides and the location of American troops in Vietnam during the Vietnam war. We describe both primary and secondary databases and methods for linking herbicide usage and troop location data. We also discuss problems of misclassification of exposure and their implications for epidemiological and clinical research.

Part II is devoted to surrogate measures of exposure that have been used in health research studies of Vietnam veterans. We discuss the advantages and limitations of such surrogates and provide a context for comparison between the exposure opportunity indices available by direct utilitization of contemporaneous military records and their derivatives. We also discuss rather extensively our evaluation of the CDC's study of serum 2,3,7,8-TCDD residues in a group of several hundred Vietnam veterans. This discussion is included here because the surrogate study with serum TCDD has been hypothesized by the CDC to be a "validation: of the utility as an exposure opportunity measure of the military records described here. That study has served as the basis for the abandonment of governmental epidemiological investigations which utilize the military records database. We thus believe it necessary to explore both the credibility of the hypothesis and the results obtained in the study.

Part I
Military Records of Troop Movement and Herbicide Usage

Battlefield Records Management and Its Relationship to Agent Orange Research

The accumulation and preservation of military records is a highly organized management function which serves many historical, legal, and financial purposes as well as for research and development. A brief history of records management prior to, during, and especially after the Vietnam war has been given by Christian and White (1), some of which is summarized here.

When the U.S. military presence in Vietnam began to build in 1965-66, the U.S. Army Command, Vietnam, took the first steps to establish a records program to protect the growing volume of information. A records headquarters was established at Okinawa in 1968, and an effective records management program put in place by 1969, one of whose tasks was coordinating the flow of records from various field headquarters generated by the battalion-level officers who were responsible for unit records. In the Fall of 1970 the Army Headquarters staff went to Vietnam to study in detail the entire records creation process, to hold classes and train records personnel, to brief commanders and to fully implement the program. A major achievement was identification of the Daily Journal, which documents a unit's activities for each 24-hour period, as a key record type to be permanently retained for later research; this would eventually become a decisive primary data source in tracking units.

In October, 1972, when it was obvious that the American presence in Vietnam would soon be drastically reduced or eliminated, the concept of the "Stand Down Records Retrieval Team" was introduced, and plans were developed to organize and ship out war records. By March, 1973, the Army had shipped over 10,000 linear meters of records to its interim processing point in Hawaii for subsequent transfer to permanent archival in Washington. It is believed that only about 800 meters remained in Vietnam after the final American withdrawal and were abandoned.

When Agent Orange became a topic of public and scientific concern in 1978, the Office of the Adjutant General of the Army anticipated the need for troop data in future scientific studies. In 1980 it established the Army Agent Orange Task Force (AOTF) with a staff of three researchers who were experts in records management and an eventual staff of 27, including clerical personnel. General orders were issued to prevent destruction of Agent Orange related records, and Army records managers around the globe were canvassed for reports on relevant data holdings.

In May, 1980, when it appeared that the Veterans Administration would conduct extensive epidemiologic research on health effects of Agent Orange, the AOTF began a series of records research projects to determine the feasibility of reconstructing the movements of combat battalions in Vietnam. Two Army and two Marine battalions were randomly selected and their records thoroughly scrutinized, and from this effort it was established that locations of individual units down to the company level was perfectly feasible, given enough material resources.

Primary Military Data Available for Scientific Research

The Army Agent Orange Task Force subsequently became the Army and Joint Services Environmental Support Group (ESG) with a records maintenance and retrieval mission encompassing all four military services plus Coast Guard (which had a small contingent in Vietnam). The ESG developed procedures for locating and tracking military units in Vietnam "to order," specifically for epidemiological studies. One of their initial "clients" was the Veterans Administration; later work was done under contract to the Centers for Disease Control, which took over the VA studies in 1983 at the behest of Congress. It continues to carry out similar missions in 1993.

The ESG's tracking procedures rely on a variety of data sources which include not only the Daily Journals but at least a dozen other types of records. Many of these are described in Table 1, which lists the primary data sources described in this paper. Two data sources worth special mention are the Operations Reports and Lessons Learned (ORLLs), which describe significant actions and their locations, and Troop Strength Estimates, which are official authorizations for personnel allocation. ORLLs are an especially useful tracking tool because they contain precise coordinates of companies and often platoons as they operated against the enemy in the field. The troop strengths can be used to precisely define sizes of populations "at risk" for exposure, and therefore to determine sample sizes of epidemiological studies.

It is important to realize, moreover, that these data represent a large segment of the computerized data available on the Vietnam war. This war is perhaps the best documented military engagement in history. It occurred concurrently with the development of computers, and at a time when the Department of Defense had made development of electronic information systems a priority. During the conflict ended, the US Army Combat Developments Command conducted an inventory of the data available. The product of that effort was a lengthy report covering hundreds of potential data sources. (2) Examination of this report demonstrates the extensive data holdings available.

Secondary Military Data Available for Scientific Research

During the thirteen years since the AOTF/ESG was established, it has assembled several sizeable databases for use by Federal agencies engaged in Agent Orange research. The most important of these are listed in Table 2.

A key database upon which nearly all others depend is the descriptor system for military units, because troop location data are organized on the basis of the military unit. Every member of the Armed Services was assigned to one of about 6,000 units, and most served in more than one unit at different times. The ESG created a 7-digit Unit Identification Code (UIC) which makes it possible to represent an individual's military history by listing chronologically his/her UIC codes along with service dates for each unit. The first digit represents the branch of service (1 = Army, 2 = Marines, etc.) and the remaining digits specify a named unit. These codes were assembled into a master file called the UICLIST.

Table 2 also lists the derivative data files for the three largest studies for which the ESG provided data: (1) VA-Army mortality study, (2) VA-Marine mortality study, (3) CDC follow-up study. These contain a total of nearly half a million troop location records. Also included in Table 2 are the two major herbicide spray files, comprising over 22,000 records described more fully in the next section.

The databases summarized in Table 2 may be considered secondary sources, because they are derived from the primary military records (see Table 1). These are resources that could be used in future epidemiologic studies, subject to further evaluation for suitability to a specific purpose. As an example, we have extensively edited and re-organized several of them for rapid evaluation of exposure for claimants to the Agent Orange Veteran Payment Program (AOVPP) (3).

Finally, we list in Table 2 two health-outcome data bases, one developed by CDC for its Veterans Experience Study (VES) (4), and the other assembled by us as part of the AOVPP. The CDC data were developed from its study of over 14,000 veterans, and contains over 9,000 records based on medical examinations and/or telephone surveys that link health outcomes with Agent Orange exposure scores calculated using a formula similar to our own (see below). The AOVPP data consist of microfilmed medical records and death certificates filed in support of claims to the Class Action Suit, with computerized exposure scores.

Herbicide Spray Data

Origin of herbicide data base: Between 1961 and 1971 the U.S. Military sprayed over 19 million gallons of herbicides on South Vietnam, of which nearly 12 million gallons was Agent Orange. Public concern over potential harmful effects on the indigenous population led to a Congressionally funded study by the National Research Council, which found evidence of substantial ecological damage (5). Wartime conditions, however, precluded a comprehensive assessment of health effects on the population. Possible effects on American servicemen were given little consideration. All herbicide spraying ceased in 1971.

An important product of the NRC study was a compilation of herbicide spray records from Operation Ranch Hand, the US Air Force herbicide spray program. The NRC organized the data into a file, known as the HERBS tape, which contained coordinate points for more than 6,200 missions flown by fixed-wing aircraft, and included date, type of herbicide, gallons applied, and purpose of mission. In the early 1980's the Environmental Support Group at the Pentagon assembled a supplementary tape (the Services HERBS tape) consisting of helicopter, backpack, and other smaller-scale spraying. We have created a composite HERBS data file from these two sources that brings the total information base to over 2,600 individual military spray missions.

Structure and content of herbicide data base

Each record in the composite HERBS file contains the following information: date of spraying, UTM (universal transverse mercator) coordinate, type of herbicide, number of gallons, mode of application, type of aircraft (if appropriate), and where available area sprayed. For aircraft-flown missions, the file also contains connectivity indicators which enable one to trace the path of spraying (see Table 3).

We have previously described the patterns of herbicide usage in Vietnam (6). Figure 1 shows the total number of gallons of each of the three herbicides (Orange, White, and Blue), and the number of application missions by type. Defoliation of jungle constituted the most important herbicide use, but millions of gallons were used for destruction of food crops (Fig. 1a) and thousands of gallons were used to clear communication lines, waterways, and base camp perimeters (Fig. 1b). Figure 2 shows the total number of gallons of herbicide applied, by agent, for each quarter from 1965 through the end of the spraying in 1971.

Over 1,000 missions were for clearance of base perimeters. About half of these involved Agent Orange (about 135,000 gallons). While this represents only about 1.1% of the 11.8 million gallons of Agent Orange sprayed in Vietnam, much of it was applied by individual servicemen using portable backpacks, directly on or adjacent to troop installations, and therefore may contribute disproportionately to troop exposure when compared, for example, to spraying from C-123 planes.

ESTIMATION OF EXPOSURE BY LINKAGE OF TROOP MOVEMENT WITH HERBICIDE SPRAY DATA

Estimation of exposure of an individual veteran to Agent Orange is a straightforward procedure which geometrically compares his known locations with the UTM coordinates for spray locations contained in the combined HERBS files. This can be expressed in one of two ways: (1) as a discrete number of "hits," which are counts of the number of times a veteran was located within a specified radius (e.g., 2 km) from any of the spray locations on the HERBS file at times when spraying occurred; and (2) as a continuous exposure index that takes into account the actual distance from each spray and the time elapsed since the spray occurred. The discrete indices simply count the number of likely exposures that could have occurred within a specified radius of a veteran's location, while a continuous index can take into account concurrent exposures plus potential exposures from residual herbicides from all previous spray missions that ever took place near any of his locations.

An integrated exposure index which has the above mathematical properties was published by us in 1986:

$$E_j = C_0 \sum_{ij} 1/(D_{ij}) \int_{t_{1,ij}}^{t_{2,ij}} \exp(-\lambda t)\, dt$$

where C_0 is an arbitrary constant, D_{ij} is the distance from the veteran's ith known location to the jth coordinate in the HERBS file, $t_{1,ij}$ is the first date he was stationed at location i, and $t_{2,ij}$ is the date he left it. λ is the time constant.

This formula effectively counts the number of hits, weighting each by two factors: a reciprocal distance factor and an exponential decay time factor. The reciprocal distance factor gives higher weight to closer "hits" in the summation. For computation convenience, the sum is restricted to all distances less than or equal to 15 km; hits at greater distances contribute negligibly to the sum. The exponential time factor takes into account explicitly the fact that once sprayed Agent Orange does not instantaneously disappear, but will persist in the environment at decreasingly lower levels as it decays. The integration thus gives higher weight to more recent hits, while "remembering" effects of past sprayings. The integral is evaluated analytically from $t=t_{1,ij}$ to $t=t_{2,ij}$, except that if the spraying occurred after time $t=t_{1,ij}$ the lower limit of the integral is set to the actual date of spraying.

Choice of a first-order decay law is a conservative approximation because it assumes a more rapid environmental disappearance than might actually have occurred (soil samples at Seveso showed a half-life that actually increased with time). Sensitivity analyses showed that relative rankings of veterans' exposure scores changed very little with large changes in lambda.

Figure 3 shows the distribution of exposure scores for the approximately 64,000 two-week data elements on the Command Post List, where each element represents one company-sized unit for an average of two weeks each. Seven percent of the units had a score of exactly zero, 43% had a score greater than zero but no greater than 0.1 (on an arbitrary scale), and the frequency distribution fell off rapidly. Veterans whose exposure scores ranked in the highest 2% of all scores had values of at least 1.85 or nearly twenty times the highest score in the least exposed half of the population.

Methodological Issues in the Use of Secondary Military Data

The chief methodological issue in application of these derivative data sources stems from the fact that the primary source material describes locations of groups of people (i.e., military units) and not individuals. Suitability for epidemiologic use thus reduces to the question of whether an exposure likelihood score computed from the known locations of a military unit may be reliably applied to each of the individuals who served in that unit. If the components of a unit (e.g., companies within battalions) are dispersed in the field during their tours of duty, company locations may give more accurate exposure scores than battalion locations. However, the magnitude of possible exposure score errors which might arise from such dispersions should not be exaggerated.

First, while there are always exceptions, it is generally agreed by military records experts that field companies could be expected to stay together, especially on maneuvers that brought them into contact with opposing forces, where their locations would be carefully documented. Secondly, the locations for many companies on maneuvers can often be ascertained with additional records research, and their scores calculated more accurately. Most of the troop location data in Table 2 on III Corps battalions contain individual company location data.

A third important issue is the extent to which the data base locations for a unit, whether company or higher, represent its true locations. This problem arises because the primary data sources sometimes contain multiple and occasionally conflicting entries for small units. In such cases, ESG has exercised judgment in selecting the most "typical" location for a unit. These

cases, ESG has exercised judgment in selecting the most "typical" location for a unit. These decisions were not haphazard, but were based upon intimate knowledge of military operations and the likely deployment of field personnel.

The "Gaps" Problem. The requirement posed by CDC that daily locations be available for all battalion locations unnecessarily created an issue of "gaps" which, in a way, has come to haunt this database. It is necessary to understand the extent of coverage, to evaluate what a gap is, its implications for misclassification of exposure and, given all these considerations, how much usable data still remains for epidemiological investigations.

The ESG defines a gap simply as "no location for one day for one unit." Some gaps are result of lack of movement -- if units either permanently located at a base camp, or combat units did not move -- there was no need to report their locations daily. Such gaps are even now easily filled by consultation with the written records described in Table 1 -- a task that to a large extent has been carried out in the past several years in support of the exposure evaluation of the AOVPP.

A second, more serious type of gap results from the separate movement of units, either companies or platoons, away from their sister units for which data are available. Some of these gaps may be filled from records, but others may not be. Such data need not be considered unusable: it can often be readily documented that no herbicide application took place during the dates in question, or within a defined area of practical importance, say 15 kilometers, of the recorded location of the sister unit. Platoons and companies did not wander through the jungles of Vietnam at will. They rarely moved more than 8 km in a day. Indeed, even those soldiers whose duties included extensive jungle excursions, as with some Special Forces, were typically not expected to travel greater distances.

Because of the daily data collection requirement placed on the ESG by the CDC, this seemingly excessive amount of troop movement data in the secondary CDC data files has led us to develop systematic data reduction methods for the AOVPP files. Most often the data were simply redundant and the large number of exact duplicates could be removed. Where there was a meaningful location conflict (e.g. greater than a few dozen meters), it was usually possible to refer multiple daily records back to ESG staff for refinement or selection of most probable unit locations. In most instances, based upon duties and assignments, the range of possible movement for an individual unit was just not very far and it could be predicted that the likelihood of entering or leaving a sprayed area would not change on a day to day basis. In such cases minor inaccuracies in locations would have no effect on health outcome studies.

The opposite situation, where data were missing for periods of time, usually arose because a unit literally remained in one place, often for several months, and intermediate location reports were not considered necessary. These were readily filled in.

Based on our experience, we have concluded that many so-called gaps or inconsistencies in the secondary data sources are minor and should not seriously affect the accuracy of epidemiologic studies. Indeed, we have developed methods in the AOVPP for imputing reasonable locations and exposure scores where some data are missing, such as substituting average battalion locations for companies, or utilizing the highest computed exposure among companies whose locations are known for one whose location is not during a particular month. Numerous variations of these imputation schemes are possible which do not lead to serious misclassification of relative ranks of individuals.

Finally, we recognize that there will always be a small proportion of units for which data will always be incomplete: some gaps are real and give rise to questionable exposure scores. There are several choices in this situation, ranging from exclusion of such units from further epidemiologic studies to acceptance of misclassification, which would almost certainly be in the conservative direction of underestimating exposure.

Quality of ESG data

The data extraction and management activities of the ESG are governed by extensive quality control procedures that include review of 5% of records abstracted in the morning and 5% abstracted in the afternoon each day. Key entry quality is subjected to similar review measures. Discrepancies of gaps are reviewed by a two-person team and often resolved by further data research or exercise of judgment.

The ESG's operations and particularly QC measures were reviewed by an Institute of Medicine Advisory Committee on the CDC Study of the Health of Vietnam Veterans. In a report dated March 7, 1986, the Committee declared itself "satisfied that the ESG is capable of determining locations and filling gaps using a contextual approach, and notes that the ESG exhibits a high degree of competence in recording data gathered from these activities." (7)

Finally, in our own work developing the AOVPP data base for exposure evaluation we have subjected the ESG data to extensive cross-checks. Through internal checks we have verified that most companies were within expected geographic proximity to each other and to related units on specific dates, and that their movements are synchronous and reasonably parallel. The ESG data are also highly consistent with published descriptive sources on the Vietnam military experience, such as published Army historical reports, and unpublished troop strength reports.

Part II
Use of Surrogate Measures for Exposure to Herbicides

Table 3 enumerates a variety of surrogate measures of herbicide exposure that have been used in various studies. Their advantages and drawbacks are discussed and it can be seen that few are quantitative and all prone to extensive misclassification.

The use of biomarkers -- TCDD in adipose and serum -- is another possible exposure measure. However, as with most retrospectively collected exposure measures used in epidemiologic or clinical research, there are serious methodological problems attached to its use. The primary problem associated with serum and adipose TCDD measurements to define exposure to herbicides among Vietnam veterans is the long period of time that now has passed since the actual exposure may have occurred. This severe problem is complemented by insufficient knowledge about the kinetics of TCDD metabolism and storage, thus making extrapolation of current levels of TCDD to past exposures extremely difficult, if at all possible.

The "Validation Study": The use of serum TCDD as a measure for herbicide studies in Vietnam veterans has been reviewed by the Institute of Medicine and its conclusions presented in a report by the Advisory Committee of the CDC Health Study. (8) The Committee emphasized the problems of extrapolation of current values to past exposures, a conclusion endorsed by the CDC itself (9) and warned against overbroad generalizations and conclusions based on the results of this study.

The difficulties in extrapolation of current values for historical exposure purposes is borne out by the data published by the CDC in its full report of the serum study of Vietnam veterans, the so-called "validation" study. (4) In order to confirm the utility of the use of current serum samples, the CDC hypothesized that the storage of TCDD in serum would obey first-order kinetics. The IOM Fifth Letter Report fully discusses the limitations of this assumption. However, from a chemical perspective one could perhaps experimentally justify a first-order kinetics assumption if the results of half-life calculations based on two measures separated in time did produce the same half-life, within experimental error associated with the actual chemical measurement. When the CDC, however, calculated the half-lives for each of the 36 individuals for whom pairs of data were available, the calculated half-lives ranged from negative (4 out of 36 had higher TCDD levels after 5 years), to 2 years, to nearly 1000 years.

On the basis of the lack of correlation between the calculated half-life and the initial serum TCDD concentration, the CDC concluded that TCDD decay followed first-order kinetics,

since a well-known property of any first-order reaction is that the half-life when measured over time is independent of initial concentration. This conclusion was an error, however: in a first-order reaction concentration independence is a necessary but not sufficient condition. It is also required that repeated measurements agree with each other within the precision of the experimental method. Considering that the measured half-life ranged from four negative values (out of a total of 36 measurements) to 743 years, it would stretch scientific judgment to suggest that the latter condition was met. The CDC's assumption of first-order kinetics remains unjustified, as the IOM indicated in its evaluation. It is inappropriate to contend that a seven year or any other half-life has been scientifically established by this study or this calculation.

It is especially interesting to observe that one-fourth of the samples had a half-life slightly more than 4 years. This observation carries a particularly important implication. A half-life shorter than 7 years would, of course, mean that many soldiers who may have been exposed to TCDD during their service in Vietnam and would no longer be expected to have elevated levels of TCDD more than 15 years post-exposure. Thus the presence of TCDD could indeed serve as an indication of earlier exposure, although the exact level could not be determined because of insufficient kinetic data. But the absence of TCDD could not rule out earlier exposure. This conclusion was reached by the IOM Committee and by Kahn, an independent researcher who has studied adipose TCDD residues among Vietnam veterans. (10)

Unfortunately, the use of serum TCDD as an exposure marker had been hypothesized by the CDC to serve as a validation for the accuracy of the extensive military records described above. This is an unfortunate hypothesis because: a)the serum measure is not accurate this late in time; b)military records have a valuable place in epidemiological and clinical research. The two methods need not be placed in competition. Each has a logical utility.

Despite the difficulties in extrapolating current serum values for historical exposure purposes, some useful data is available from the so-called "validation" study. However, great caution must be used in interpreting the "validation study" since it is largely a study of an unexposed population. The cohort was assembled as follows. There were 14,473 Vietnam veterans listed in CDC data files and who had been chosen for the main Agent Orange Exposure Study without regard to potential ranking as to likelihood of exposure to Agent Orange. There were 9,727 living veterans from this group who had computable Agent Orange "hit" scores of which 994 were invited to participate in the Validation Study. Blood was obtained from 646 men. The distribution of "hits" among the study participants was as follows:

298 were 0 "hits"
157 < 5 "hits"
191 5+ "hits
646

In an attempt to increase the sensitivity of the study and compensate for the small number of potentially "exposed" study members, two re-analyses were carried out by us: one was restricted to men whose serum TCDD levels placed them in the upper quartile and the second further restricted to men in the upper decile. These restrictions were based on the reasoning that men with the lowest TCDD levels could either have low levels because they were not exposed, or because they had already excreted or metabolized the TCDD which they had absorbed, or because the military records did not accurately predict their exposure status. Thus, because of these varied possibilities, the low TCDD scorers represented a poorly defined group for study and hence maximized the possible misclassification problem. On the other hand, men in the upper quartile or decile of exposure had obviously not exceeded the time required for TCDD to decay to background, (although their metabolic rates may still have differed within the group) and therefore represented a group with a smaller likelihood of misclassification.

A correlation coefficient was calculated between each of the CDC's six Agent Orange exposure scores and the blood dioxin level for the 646 men in the Validation Study for whom these data were available. The correlation coefficient was not significantly different from zero for 5 of the 6 exposure measures; however, a very weak correlation (.09) between blood dioxin and the "unknown agent hits" score was significant. This could have been due to chance, and in

any event would likely be of no biological importance. The correlation coefficients among the 173 men in the upper quartile, however, were both substantial (.17 - .34) and statistically significant. Finally, the correlation coefficients of the 65 men in the upper decile (10%) were higher still (.27 - .44) and were all significant. The four exposure measures were the unknown hits, Agent Orange plus unknown hits, the unknown E3 score, and the Agent Orange plus unknown E3 score.

[As background, a herbicidal agent was classified as "unknown" when the specific agent used was not recorded on the record. However, the most frequent agent used at the time was Agent Orange and many of the record keepers simply failed to note the name. In no circumstance would the spray have been other than a herbicide. Insecticides were never erroneously coded as herbicides, as implied in the CDC "validation" report.]

A simple regression analysis was also carried out using the six exposure measures to predict the blood dioxin levels. The results were consistent with the correlations. That is, for the entire group of 646 men, only the unknown hit score was a significant predictor of blood dioxin. However, when the 473 men with the lowest blood levels were removed, and the prediction equations applied to the upper 25%, the same four exposure scores as in the correlation analysis were now significant predictors of blood dioxin level. Further restricting the regression analysis to the upper 10%, the prediction coefficients were statistically the same as those for the upper 25%, while the significance levels became smaller. These data are summarized in Table 4.

The regression analysis was to a large extent "driven" by a single point, that of a veteran whose serum TCDD concentration was 45.3 ppt. However, this score could not be considered an "outlier" since it was the score of the veteran who suffered 115 direct "hits", the highest number of hits calculated for any veteran in the study.

Further Cohort Selection Considerations:

In exploratory studies of correlates of exposure, it is desirable to investigate as wide a range of exposure as possible so as to maximize signal-to-noise (11). It may therefore seem remarkable that 70% of the 646 validation subjects experienced fewer than five hits; that is, fewer than one-third had even a minimal potential for exposure.

One explanation for the relatively low number of men with more than 5 "hits" in the CDC study was the selection criteria used. First, since the names were assembled without regard to likelihood of exposure, it is to be expected from the distribution shown in Figure 3 that the number not likely to have been exposed would greatly exceed the number of exposed. Second, the CDC used a set of eligibility criteria which would tend to eliminate those with greater exposure likelihood. These criteria included a single tour of duty in Vietnam, a rank restricted to E1-E5 and service in a "line" company. Many men, sometimes more than 85% of those submitted by the ESG to the CDC as potential study population candidates each month were rejected on these bases. (12) The single tour of duty requirement, in particular, severely limited exposure opportunity potential, since it is obvious that a lengthy exposure is incompatible with a short tour of duty.

In order to maximize the ability of their study to determine whether a correlation between serum dioxin levels and "exposure" determined from military records existed, CDC should have included a sufficient number of heavily exposed veterans in the study. For example, the CDC could have used the available data in which it had ranked battalions by likelihood of exposure (13,14) to choose men from the more heavily exposed groups.

Five battalions (numbers 2, 6, 10, 11 and 22) represented 79% of all the subjects in the CDC study and were the military units in which the veterans spent the most time during his single tour in Vietnam. However, the data supplied by ESG to the CDC in the pilot study which served as the basis for the "validation" study, ranked the six "highest" exposure battalions as numbers 50, 43, 2, 22, 10 and 20. Battalion 11, which was heavily represented in the "validation study," was the battalion ranked lowest on exposure, while highly exposure-ranked battalions 20 and 43 of ESG's pilot study were virtually unrepresented in the "validation study." Battalion 20

had the greatest number of "hits" according to CDC calculations, 328 within 1 day and 5 kilometers. However, only 3 men who served in this battalion donated blood for the "validation" study. Battalion 43 had the second greatest number of hits calculated by the CDC, with 149. However, only 1 person from Battalion 43, Company D, donated blood to the Validation Study, and Company D of Battalion 43 was not the unit in which he spent the most time. The other battalion from ESG's pilot study that is not represented in the Validation Study is battalion 50, which was selected by ESG for the pilot study precisely because it was the highest ranked for opportunity for exposure on the list CDC sent to ESG.

The CDC, in its Interim Report Number 2, calculated that battalion 6 had the 2nd largest number of hits, 236, with 204 hits to Company A, 25 to Company C, and 2 and 3 to Company B and D, respectively. In the Validation Study, although 24% of the veterans were assigned to Battalion 6 at some time, only 55 men who donated blood served in Company A, the most heavily sprayed company. The CDC had interviewed 90 men who served in Company A but blood was only obtained from 55 of these men (61%). The majority of men who served in Battalion 6 and participated in the Validation Study served in H company, whose hits were never analyzed. 24.5% of the "validation study" blood donors were assigned to two of the battalions, 10 and 11, but these battalions are among the lowest ranking units in Table 3 of the Interim Report Number 2, scoring only 6 hits and 1 hit within 1 day and 5 kilometers, respectively.

Thus, given the correlations observed when the cohort was limited to those with TCDD above background, and the extremely questionable study population selection methods used, this study cannot be interpreted as demonstrating the inadequacy of military records in classifying veterans as to likelihood of exposure to herbicides. To the contrary, despite the methodological weaknesses of the study design and the inappropriate selection of study participants, this study is highly suggestive of a conclusion opposite to that reached by CDC, namely, that military records are indeed a useful and usable method of estimating exposure likelihood.

Future research

We have described a rich and voluminous collection of data resources from which it is possible, in principle, to reconstruct the herbicide exposure opportunities of hundreds of thousands of veterans. Our principal scientific concern has to do with the accuracy of such assignments, and questions of direction and degree of misclassification which must be adequately resolved before quantitative exposure assessment methods can be routinely applied in epidemiologic studies.

Before these methods can be used with complete confidence for research, further studies should be conducted that examine the limits of the methodology. In particular, sensitivity analyses of the extent to which the relative exposure rankings for individual veterans are altered by changing the assumptions used in constructing the exposures for their military units. For example, one could hypothesize specific "error" in the recorded locations of troops and/or of spraying and determine at which point such "errors" would lead to the reclassification of a veteran's exposure group. This error band could be added to the database and included in the error estimates of future studies. Some units might be eliminated if they were found to be particularly sensitive to such misclassification. On the other hand, units with "gaps" might be included because imputation of locations might be found to introduce no reasonable likelihood of misclassification. Thus for companies and battalions where gaps exist for a portion of their stay in Vietnam, it may be possible to identify additional significant time periods where there are no gaps whatever, covering large numbers of troops. It is quite likely that satisfactory exposure data could thus become available for many units previously rejected by the CDC through inappropriate selection criteria.

We have already taken some steps in this direction within the database that we have established for the AOVPP. Our experience with handling of the records of tens of thousands of veterans has further given us confidence that the likelihood of being switched from "low/no" exposure to "high" is rather remote. This is intuitive when one examines the distribution in Figure 3.

Finally, it should be recognized as a matter of principle that it is not necessary to know with infinitesimal precision the location of every single soldier in Vietnam in order perform a study which meets prevailing standards of current epidemiological practice. There are tens of thousands of potential study subjects available and controls can be located with ease since a greater number of Vietnam era veterans did not serve in the war theatre than the number who did. Further, this paper has not addressed the study potential of "special" exposure situations, such as service in the "Chemical Corps" or service in an area where a recorded massive accidental exposure occurred, such as emergency "dumping" of herbicide by spray mission aircraft.

The opportunity for epidemiological and clinical research is great and the underlying support system of military records provides a sound firmament for the research effort.

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Table 1
Databases Available for Scientific Research - Based on Primary Sources

The data described in this table are the raw data collected by the armed forces during the course of its service in Vietnam

Database Description	Precise Location Data Include: Data Entries	Military Units
Battalion Daily Journals: To record significant actions and precise locations of the maneuver companies. Emphasis placed on fighting units	UTM locations-daily by operations officer	Battalions field companies headquarters company
Situation reports (SITREPS): contain information about locations of battalions and their companies, and contain notations on daily combat actions	UTM locations daily	Battalions field companies headquarters company
Operations Reports and Lessons Learned (ORLL): delineates significant actions and their locations; contains a section on herbicide operations	UTM quarterly reports by Division Commander	Each element of the Division and the staff
Command Post Lists: Provide command locations	UTM and valid dates	Data to the battalion level
Station lists: base locations	UTM quarterly	To the battalion level
Command Chronologies: A collection of all records and information that reflects significant occurrence		All units in command
Combat Operations After Action Reports: Detailed information regarding major battles	May contain location data	All units in command
Unit Histories: Summarize information available from other databases and cover a broad scope of functions about the unit	Written by unit historian	All units in command
Morning Reports, Muster Rolls and Unit Diaries: Personnel related data containing complete rolls of those present, transferred in or out, casualties and other notations affecting personnel status	Unit commanders	Each company, battery or detachment
Troop Strength Estimates: authorized allocation of personnel per unit; frequently revised to reflect actual (vs. authorized) strengths	Monthly with geographic location of headquarters	Generally on battalion level

Table 2
Secondary Data Sources of Herbicide Spray and Troop Location

In order to provide documentary support to researchers, veterans and others in need of precise information on troop movement, herbicide exposures and other relevant military information, the Department of Defense collected and examined hundreds of thousands of documents from databases listed in Table 1. Additional data has been collected by the Exposure Evaluation Unit of theAgent Orange Veterans Payment Program, U.S. Eastern District Court. Some of these databases are described below.

Database Description	Approx. No. Data Records	Type of Records
UICLIST: Master code list, consisting of 7-digit code, with first digit signifying branch of service, created to facilitate development of secondary database	6,000 units	Created by US Army Agent Orange Task Force, later US Army & Joint Services Environmental Support Group, to facilitate development of secondary databases
	Troop Location Data:	
III Corps Batallions	300,000	Company and batallion locations for 50 batallions, 1966-69, abstracted by CDC; weekly or more often
Army mortality file	80,000	Company and batallion unit locations for men in VA Army mortality study
Marine mortality file	40,000	Company and batallion unit locations for men in VA Marine mortality study
AOVPP location support file	450,000	Merged file of 3 above databases, with many location gaps filled in and units with stationary assignments added; assembled under auspices of Agent Orange Veterans Payment Program
	Herbicide Spray Data	
HERBS tape	17,000	Fixed-wing aircraft: Spray coordinates, date, gallons, mission purpose, type of herbicide
Services HERBS tape	5,000	Helicopter, backpack, truck: Spray coordinates, date, gallons, mission purpose, type of herbicide
	Health Outcome Data	
CDC Veterans Experience Study (VES)	14,473 on file; 9,727 scorable with existing data	Telephone interviews, medical records, and exposure scores from CDC study
AOVPP	55,000	Medical records, death certificates, military records, computerized microfilm files

Table 3
Surrogate Measures Of Herbicide Exposure

SURROGATE	ADVANTAGES	DRAWBACKS
Any Vietnam-Era military service vs. civilian	Easily verifed	60% of Era veterans not in Vietnam, no opportunity for exposure
Military service in Vietnam vs. elsewhere	Agent Orange used almost exclusively in Vietnam	Use was not random; probability of exposure < 20%
Branch of service: Army vs. Navy, etc.	Army and Marines most likely exposed, Navy lessy; AF Ranch Handers heavily exposed	Even in Army, prob. of exposure was low; some brown-water Navy were exposed; AF exposure at some bases was very high, others unexposed; AF ground crew exposed to leaks
MOS (Military Occupational Specialty), e.g. rifleman, engineer	Identifies herbicide & chemical handlers; some occupations (e.g. clerical) presumably unexposed	No. handlers was small; other specialties correlate poorly with exposure
Combat vs. support roles	Combat troops more likely to be exposed	Most combat troops were not exposed, prob. of misclassification high
Military region: I Corps, II Corps, etc.	III Corps was most heavily sprayed, I Corps less	Saigon (not sprayed) and Iron Triangle (heavily sprayed) both III Corps; spraying was not random in other Corps

Table 4

Correlations between records-based exposure scores and serum TCDD levels (data from ref. 4)

Exposure Measure	Pearson Correlation Coefficient	No. Subjects (a)	Pearson Correlation Coefficient	No. Subjects (b)	Pearson Correlation Coefficient	No. Subjects (c)
Agt. Orange E3	-0.05	646	-0.06	173	-0.14	65
Unknown Agt. E3	0.06	646	0.22**	173	0.32*	65
Agt. Orange E3 plus Unknown E3	0.04	646	0.19*	173	0.27*	65
Agt. Orange hits within 10 km	-0.04	646	0.00	173	-0.07	65
Unknown Agt. hits within 10 km	0.13***	646	0.38***	173	0.47***	65
Agt. Orange plus unknown agt. hits within 10 km	0.06	646	0.24**	173	0.29*	65

(a) All study subjects
(b) Subjects in highest TCDD quartile
(c) Subjects in highest TCDD decile

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

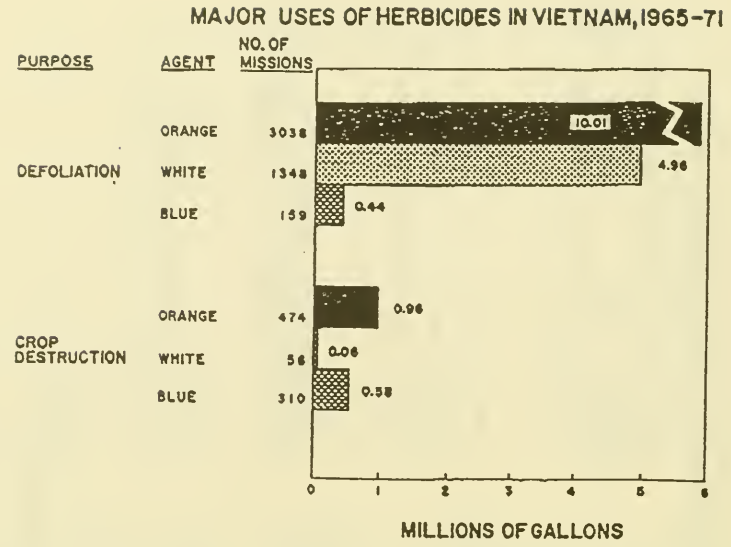

Fig. 1a Quantities of Agents Orange, White, and Blue used in defoliation and crop destruction missions in South Vietnam, 1965–1971.

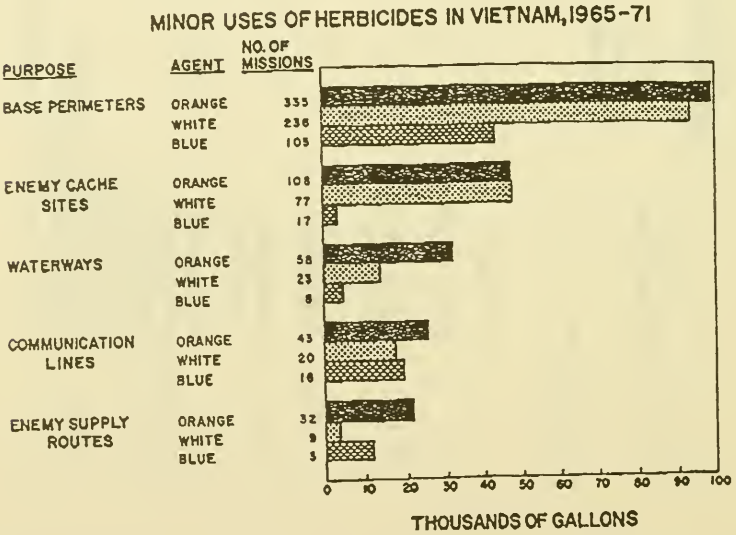

Fig. 1b Quantities of Agents Orange, White, and Blue used in five minor types of missions in South Vietnam, 1965–1971.

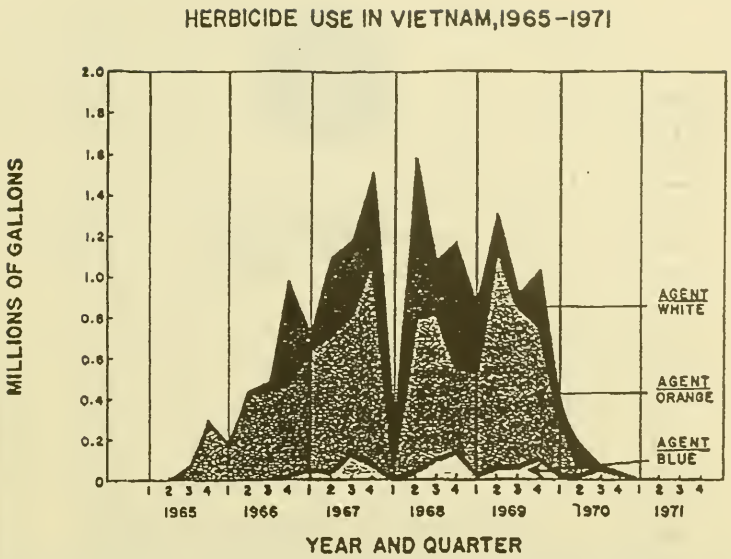

Fig. 2 Quantities of three herbicides used in South Vietnam, 1965–1971, by calendar quarter.

FIGURE 1

AGENT ORANGE EXPOSURE

STATEMENT OF
THE AMERICAN LEGION
1608 K Street, NW
Washington, DC 20006

from

RICHARD S. CHRISTIAN, DEPUTY DIRECTOR FOR
RESEARCH AND TECHNOLOGY ASSESSMENT
NATIONAL VETERANS AFFAIRS AND REHABILITATION COMMISSION
THE AMERICAN LEGION

to the

COMMITTEE ON VETERANS AFFAIRS
UNITED STATES SENATE

on

AGENT ORANGE

NOVEMBER 2, 1993

Mr. Chairman and Members of the Committee:

The American Legion appreciates this opportunity to comment on recent changes to Department of Veterans Affairs (VA) regulations governing presumptive service connection based on herbicide exposure and to express our views of VA's response to the National Academy of Sciences Report - Veterans and Agent Orange, Health Effects of Herbicides used in Vietnam, released on July 27, 1993.

The American Legion supports the recent administration decision to award compensation to Vietnam veterans suffering from Hodgkin's disease, porphyria cutanea tarda (PCT), respiratory cancers (lung, larynx and trachea) and multiple myeloma. This decision tracks closely with recommendations made for years by The American Legion. We still have a long way to go but we are starting to make some progress.

Public Law 102-4, 105 stat. 11 (1991) added 38 U.S.C. 1116 to establish presumptive service connection for veterans who served in Vietnam who develop to a degree of 10 percent or more, non-Hodgkin's lymphoma, soft-tissue sarcoma and chloracne. Further, Public Law 102-4 mandated that the Secretary of Veterans Affairs enter into an agreement with the National Academy of Sciences (NAS) to review the scientific evidence to determine the association between exposure to herbicides sprayed in Vietnam and each disease reported to be associated with herbicide exposure. The NAS accomplished its task and concluded that there is an association between exposure to herbicides sprayed in Vietnam and the later development of non-Hodgkin's disease, soft-tissue sarcomas and chloracne for which the VA previously began paying compensation. In addition, the NAS determined an association between exposure to herbicides sprayed in Vietnam and the development of porphyria cutanea tarda (PCT) and Hodgkin's disease. Proposed rules for the two additional diseases were published in the Federal Register on September 28, 1993.

The NAS determined that there is suggestive evidence of an association between exposure to herbicides and respiratory cancers (lung, larynx, trachea), prostate cancer, and multiple myeloma. While the VA concurred with the NAS finding of association between exposure to herbicides and respiratory cancers and multiple myeloma, prostate cancer was not recommended for compensation by the VA's Agent Orange Task. On August 17, 1993 The American Legion in a letter to the VA's Task Force strongly recommended that prostate cancer as well as the respiratory cancers and multiple myeloma be included in the VA's decision for compensation. The American Legion believes that it is at least as likely as not that a statistical association exists.

Mr. Chairman, based on several scientific reports concerning the adverse effects of exposure to Agent Orange, there are thirty cancers and diseases which should be reviewed and considered for compensation. The Environmental Protection Agency (EPA) recently reviewed the same studies the NAS reviewed on chemical workers and came to a definite conclusion, as part of its ongoing efforts to evaluate the risks of TCDD, dioxin, a byproduct of Agent Orange. After undergoing extensive public and expert review, and after open workshop meetings, the EPA's second draft report on human epidemiology (EPA Publication No. EPA/600/AP-92/001g, June 1993) states:

> Other TCDD related normal effects, including immune suppression, may result in multi-organ sensitivity and may contribute to the overall increased mortality from all malignancies combined seen in all four cohort production worker subcohorts with higher estimated TCDD exposures...These increased relative risks, while not large (10% to 70%) are consistent and are either statistically significant or of borderline significance. While no one tissue site can account for this observed increase, lung cancer is also increased in three of these.

These conclusions should be incorporated by the VA, and used as a basis for compensating Vietnam veterans exposed to Agent Orange for cancers at any site.

Peripheral neuropathy was recommended by the VA's Environmental Hazards Committee to the Secretary and proposed rules were published in the Federal Register March 1991, to compensate our nation's Vietnam veterans who are suffering from this disease. The proposed rules contained restrictions and would limit compensation to Vietnam veterans who were diagnosed with peripheral neuropathy within 10 years of exposure to Agent Orange. The American Legion strongly opposed the 10 year window. Studies have shown that the latency period can be as long as 13 to 15 years. Also, the studies do not take into account that symptoms are insidious, sometimes not noticeable for years after they begin to appear. To date, final rules have not been promulgated by the VA.

The American Legion, since early 1978, has encouraged Vietnam veterans with conditions felt to be caused by Agent Orange exposure to file the proper forms with the Department of Veterans Affairs, in order to establish a claim for service connection of such diseases or disabilities. By filing a claim, these concerned Vietnam veterans are able to establish a claim now, so that it will be of record at such time additional diseases are determined to be caused by exposure. The Legion has consistently stated that it is the responsibility of the Federal Government, using all resources available, to determine the effects of Agent Orange on veterans who were exposed to it in Vietnam as expeditiously as possible, and to adequately compensate those individuals who have incurred disabilities as a result of such exposure.

Mr. Chairman, we will offer comment on VA's overall response to the NAS report. Immediately upon release of the NAS report, the Secretary of Veterans Affairs approved awarding Vietnam veterans suffering from Hodgkin's disease and porphyria cutanea tarda (PCT) compensation. These diseases were added to the list of diseases VA previously had recognized as being associated with herbicide exposure. The VA established a task force to review findings on diseases which NAS found only limited or suggestive evidence of an association with herbicides used in Vietnam. These conditions included respiratory cancers (lung, larynx, trachea), prostate cancer and multiple myeloma.

The VA's task force recommended and the Secretary approved compensation for respiratory cancers and multiple myeloma but not prostate cancer. While The American Legion considers this another milestone in the long road of Vietnam veterans to achieve assistance from their government, the VA Secretary should have prescribed regulations presuming service connection for prostate cancer and peripheral neuropathy on the basis of sound medical and scientific evidence that the credible evidence for the association is equal to or outweighs the credible evidence against association. The Secretary has that authority in the Agent Orange Act of 1991.

Mr. Chairman, we will offer comment on the Agent Orange research recommended by the VA. The American Legion recommends that the VA proceed with one or more epidemiological studies in order to resolve the remaining concerns of the veterans and their survivors with reproductive problems, birth defects and all other diseases reported by the NAS as having inadequate or insufficient evidence to determine whether an association exists including limited and suggestive evidence of no association. The NAS report clearly reveals that studies of sufficient statistical power may provide the answers to the diseases in these categories.

The NAS report included several research-related recommendations. The VA Secretary approved expanding the scope of the VA's Chemical Corps Vietnam Veterans Study, to include oversight by an independent non-government scientific panel. The American Legion opposes assigning oversight responsibility to the Ranch Hand Advisory Committee as suggested in the task force report. The American Legion wishes to point out that at the public meeting of the NAS held December 8, 1992, Ranch Hand scientists effectively disavowed the herbicide exposure index which has

figured prominently in numerous Ranch Hand reports reviewed by the same advisory committee the VA proposes for oversight of the Army Chemical Corps study.

The NAS report recommended that biomarkers for herbicide exposure be further developed. The VA Task Force recommendation to monitor the scientific literature in this area and solicit proposals from VA researchers engaged in related research projects does not respond to the broader question of the need for a major epidemiological study of the U.S. ground troops by a non-government organization as recommended by the NAS. The NAS clearly believes that reconstruction based on military records should receive the larger emphasis.

The American Legion recommends that the data already collected by the Centers for Disease Control in the canceled major epidemiological study of the ground troops that served in Vietnam be evaluated by a non-government organization. Further, the research carried out by the Department of Defense in tracking military units and the use of herbicide spray operational records will be a valuable resource for historical reconstruction exposure models and use in a major study. A scientifically valid epidemiological study is critical to our search for more answers.

This concludes our statement.

Vietnam Veterans of America, Inc.
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STATEMENT OF

VIETNAM VETERANS OF AMERICA

Presented By

Paul S. Egan
Executive Director

To The

Senate Veterans' Affairs Committee

On

National Academy of Sciences (NAS) Report

"Veterans and Agent Orange:
Health Effects of Herbicides Used in Vietnam"

November 1, 1993

Introduction

Mr. Chairman and members of the committee, Vietnam Veterans of America (VVA), appreciates the opportunity to submit written comments on the recently released National Academy of Sciences (NAS) review of existing scientific data on the health effects of dioxin. We view this as a critical juncture in the policy dictated to VA regarding veterans exposed to hazardous substances -- not only for the Vietnam War generation, but for subsequent groups who serve in the military. Current and future science on Agent Orange and other toxic substances will affect the future quality of life for many of our nations veterans.

We commend you, Mr. Chairman, for holding this hearing to further evaluate report findings. We have already observed that proper interpretation of this document is vital to establishing sound policy regarding VA treatment and compensation of conditions related to veterans' Agent Orange exposure. No matter how conclusive or inconclusive scientific studies and reports may be, proper interpretation of data is the key to effecting appropriate, logical and humanitarian policy.

Initial Review of Report Encouraging

A preliminary examination of this major scientific review indicates proof, for the first time, of what Vietnam veterans have charged for two decades: the Agent Orange sprayed across South Vietnam from 1961 through 1971 caused a broad array of deadly cancers and other health

hazards for Americans who served there. Finally an unbiased scientific panel has looked at the evidence with open eyes and has seen the obvious connections that no U.S. government-based study has been willing to see. This honest report, slated to be the first of several over the next few years, has already made a serious difference to thousands of Vietnam veterans and their families.

The NAS report lists diseases in four categories: sufficient evidence of an association, limited/suggestive evidence of an association, inadequate/insufficient evidence to determine whether an association exists, and limited/suggestive evidence of no association. This odd-sounding characterization stems from the scrupulousness of the scientists on the panel, who refused to use the government's usual two-step evaluation that lists diseases as clearly "caused" by Agent Orange or not "caused" by Agent Orange. Far too many studies have treated a failure to find a compelling connection as proof that no connection exists. That is bad science.

Diseases in the category of having "limited or suggestive evidence of an association" have evidence to support their association with Agent Orange, the panel says, but the studies do not bear it out as clearly as in the first category. One good study may make the connection, the report points out, but other studies fail to. The report uses the word "association" rather than "causality" because what it is identifying is a heightened risk. An individual can be sprayed repeatedly with Agent Orange and never contract any of these diseases, and a person with no exposure whatsoever can still come down with any of them. A disease with a heightened risk -- an "association" -- is one that a veteran probably would not have contracted without exposure

to dioxin while on active duty, which is why the presumption of service-connection is made.

These language choices are very important, given the government's past refusal to honor Agent Orange claims because "causality" could not be established. Just as the tobacco industry has shirked responsibility for thousands of respiratory cancer deaths because causality couldn't be proved, the U.S. government hid behind the term causality, when heightened associated risk for Agent Orange conditions was documentable.

Based on the findings of the 16-member NAS review panel, Secretary of Veterans Affairs Jesse Brown has already added Hodgkin's disease, porphyria cutanea tarda (PCT--a liver disorder), respiratory cancers (lung, larynx and trachea) and multiple myeloma (a cancer involving the bone marrow), to the list of diseases for which VA will award disability compensation. Prior to the July 27 release of the NAS research review, VA compensated only soft-tissue sarcoma, non-Hodgkin's lymphoma and chloracne.

VVA is often critical of the VA, but we want to state clearly that the initial steps Secretary Brown has taken were both appropriate and compassionate. He has not only added the most obvious of the ailments to the list of compensable conditions, he has also ordered the rapid notification of veterans known to have been denied aid for these illnesses of their eligibility for help. These steps were a logical necessity, and we appreciate the speed and the initiative with which he has taken them.

Alarming Policy Trends

While we find the NAS report and some of VA's responses to it encouraging, there have been recent actions in both the Administration and Congress which disregard some of the report recommendations, or perhaps review it with flawed interpretations. You yourself, Chairman Rockefeller, have raised concerns about the VA Agent Orange Task Force recommendations and Secretary Brown's subsequent decisions not to compensate veterans with prostate cancer, even when the NAS report cited limited/suggestive evidence of an association.

In addition, VA has determined that it would be too costly to implement some of the other NAS recommendations. Specifically, at this time the VA does not intend to expand the study of Chemical Corp and Ranch Hand personnel, or further develop biomarkers for herbicide exposure; nor does VA intend to establish a comprehensive database of veterans and military personnel with Vietnam service.

Perhaps the most troubling issue facing our members is recent legislative attempts to limit VA's authority to provide priority treatment to Agent Orange-exposed veterans. The House Veterans' Affairs Committee recently passed H.R. 3313, legislation which would limit health services to veterans who are already receiving care for an Agent Orange condition, or to veterans with the diseases listed in the first three categories of the NAS report -- those for which NAS noted sufficient evidence of an association, limited/suggestive evidence of an association, or inadequate/insufficient evidence to determine whether an association exists.

Although the intent of H.R. 3313 is to extend and expand Agent Orange and radiation treatment in light of last July's National Academy of Science report, the effect would *truncate* the Secretary's current authority to provide priority VA care to veterans exposed to Agent Orange. The NAS study did not rule out diseases for which only a limited association has been demonstrated to date, as the language of H.R. 3313 improperly assumes. Even the VA has reservations about this part of this bill. We, along with the American Legion, strongly recommend a simple extension of existing authority as adopted by the Senate Committee on Veterans Affairs, without limiting eligibility to specific diseases.

H.R. 3313 authorizes care for veterans with some diseases NAS found less than conclusively associated with Agent Orange and the bill would "grandfather" those who have diseases not covered by the bill language but who currently get care at VA. But the language would withdraw currently available health care benefits for Agent Orange-exposed veterans who have not yet presented themselves for care at VA. If the language of H.R. 3313 becomes law, many Vietnam veterans who may yet develop conditions related to Agent Orange exposure will be denied care if they're not among the lucky whose diseases are recognized in the first NAS report. This is particularly troublesome given the latency period evidenced in many veterans between exposure and disease development -- lasting 20 to 30 years or even longer as time will tell. It makes no sense to exclude veterans from VA care whose diseases may yet be found associated with Agent Orange exposure, but who will be excluded from care if this bill is enacted without amendment.

How ironic it is that VVA was encouraged by the June NAS report because it specified that current scientific data is inconclusive on various diseases, without ruling out a dioxin connection. NAS recognized that sufficient testing has not yet been conducted, not that there was no association. Now, the framers of the House bill language seek to limit veterans access to health care for Agent Orange exposure using this lack of sufficient evidence, just as the government has attempted to deny responsibility for Agent Orange illnesses since the Vietnam War ended.

The Report's Call for More Research

Why would Vietnam veterans find a report encouraging that says the dioxin in Agent Orange caused a great deal more cases of deadly illnesses than any government study has claimed? The question is not whether Vietnam veterans are at greater risk. Agent Orange-exposed Vietnam veterans are already sick, and they know why. What is encouraging is that they can finally pin responsibility for it on their patriotic service and receive the help they have been denied for so long. That is what makes the report's call for further study so important.

A legislative proposal before Congress now, offered by Senator Tom Daschle (D-SD), himself a Vietnam veteran, calls for government-funded research in Vietnam into the effects of dioxin exposure. Such research is of major importance to Vietnam veterans and their families, and indeed, to an America increasingly plagued by environmental hazards.

VVA supports such research because Vietnam provides, unfortunately, the best laboratory for dioxin exposure and health effects studies. Agent Orange was sprayed across the South and not at all in the North, so northerners provide a scientific control group without the background contamination from dioxin that most of the industrial world has. Thus there is a larger population for detailed studies, with both lower and higher exposures -- and longer ones -- than most American soldiers, which was the same reason the NAS cited industrial studies.

Research in Vietnam can perfect what we know about where Agent Orange was used and what its effects are. What we need to know about birth defects is waiting to be found there, as well as specific effects on women, which our women veterans need to know. This research needs to be undertaken soon, because the specific marker -- elevated blood dioxin levels -- needed for such study is gradually decreasing in people's bodies.

VVA recommends that President Clinton set up an Office of Agent Orange Studies under White House supervision, similar to those for AIDS and drug abuse. For $2,000,000 per year, we can get critical information that the NAS report was unable to find, because NAS reviewed studies that others have done and not enough has been done in Vietnam. It is most efficacious, we believe, for results of high quality in a reasonable time, that such studies be conducted under sole source contracts, with the following criteria:

1. The studies must be independent of government agencies. They can be performed by scientists at medical schools, universities and research institutes.
2. They must make use of scientists who have already worked in Vietnam, because

work there demands skills and knowledge that take time to develop.

3. They must include experts in both dioxins and herbicides, with professional background in both exposure assessment and health effects.

4. They must include MDs and PhDs in occupational medicine, exposure assessment and the epidemiology of dioxin and related chemicals.

5. Such research should include exposure assessment, cancer studies, reproductive studies, neurological and neurobehavioral studies, immune system studies and studies in biomarkers of exposure and sensitivity.

All further studies, VVA contends, must be funded by the U.S. government, but conducted independently. What the NAS report shows is that we were right all along in pointing to the unwillingness of every federal agency that has studied Agent Orange to admit the damage that our government has done to its own soldiers -- damage it has repeatedly shirked any responsibility for. Congress understood that when it funded this report, and we expect Congress to stand with us in making the VA responsive to its findings.

The NAS report's criticism of the study conducted by the Centers for Disease Control supports our own complaints, and demonstrates the need for an independently-contracted exposure study, with protocols and design methodology to be reviewed by NAS or some other non-government organization of equal stature. We urge Congress to take responsibility for this as soon as possible.

EPA Findings

The Environmental Protection Agency (EPA) has undertaken a reassessment of the health risks of exposure to dioxin and similar compounds, in order to "improve the research and science base and to incorporate improved research and science into EPA decisions". Based upon recent advances in scientific knowledge of the biological, human health and environmental effects of dioxin, and the mechanisms of dioxin toxicity, the EPA preliminary draft reports the following about health effects other than cancer:

> In summary, based on the results of two or more studies, recent evidence suggests that chloracne, elevated GGT levels, an increased risk of diabetes, and altered reproductive hormone levels (luteinizing hormone, follicle stimulating hormone and testosterone) appear to be long-term consequences of exposure to 2,3,7,8-TCDD. In contrast, multiple studies show possible acute effects but few chronic exposure-related effects for dermatologic endpoints other than chloracne, such as eye lid cyst, hypertrichosis, hyperpigmentation, actinic keratosis and Peyronie's disease, for liver diseases such as cirrhosis, liver enlargement and hepatic enzyme levels (LDH, AST, ALT and D-glucaric acid) other than GGT and for porphyrias, and renal, neurologic, and pulmonary disorders. Circulatory and heart diseases, reproductive outcomes, immunologic disorders, lipid levels, and thyroid function require further study before their respective relationships to 2,3,7,8-TCDD can be more definitively assessed. Studies are underway in several locations which may yield useful information regarding these outcomes.

EPA's review of current scientific data on dioxin is more comprehensive than that of NAS in two respects. NAS examined only epidemiological research, whereas EPA noted the full range of science. EPA also looked at similar compounds, rather than only looking at studies of the specific chemical makeup of dioxin in Agent Orange and herbicides used in Vietnam. We would recommend that future NAS reports accommodate the same spectrum as that of EPA, in order to more fully evaluate the complete range of scientific information.

Examples of the problems created by these evaluation criteria include birth defects, which are noted in animal tests. Few human studies, however, have provided similar results because of various study limitations. Eliminating consideration of the research done on similar compounds also cuts out a significant portion of data. Such a restriction is comparable to conducting research on the association of tequila consumption to the development of cirrhosis of the liver, without evaluating the effects of other alcoholic beverages. We recommend that EPA's methodology be closely emulated for future NAS evaluations.

VVA is very pleased to observe that while the EPA reassessment isn't yet complete, it would seem that its policy effects are already inducing appropriate agency decision-making. We note with interest the regulations proposed November 1, 1993, which will call on the nation's paper and pulp mills to reduce the level of air and water pollutants -- including dioxin. A Washington Post article explains, "The proposed regulations, which would take effect in 1995, are the agency's first attempt to devise a 'cluster' rule regulating various air and water pollutants of a given industry. Past rules targeted individual pollutants for reduction. Under the draft rules, paper and pulp mills are required to virtually eliminate discharges of dioxin into rivers by 1998; cutting dioxin releases by 80 percent in three years."

Conclusion

In conclusion, Vietnam Veterans of America presents to you a grim satisfaction, vindicated in speaking so long for veterans whose illnesses were caused and neglected by the

government that sent them to war, and which they served so willingly. A panel of courageous and honest scientists has clung carefully to the language of science, avoiding the language of policy.

It is troubling to note that it is still possible for policy-makers to interpret this data to the detriment of Agent Orange victims, as witnessed with the language of H.R. 3313. And like you, Chairman Rockefeller, we are very concerned that the VA has chosen to ignore some of the NAS research recommendations because cost considerations take precedence. We advocate legislation mandating that VA carry out these recommendations. In addition, we suggest codification of the VA actions to provide compensation for the aforementioned additional diseases, because what this Administration can give another leadership may take away.

The language of the NAS report is yours to use, Mr. Chairman and members of the Committee. We ask that you read this study with policy in mind, and that the policies you write in response to this landmark report -- and those you urge the Secretary of Veterans Affairs to write -- rely upon reason and science, and give the veteran the benefit of the doubt.

Mr. Chairman, this concludes our statement.

E. R. ZUMWALT, JR.
ADMIRAL, U. S. NAVY (RET.)

October 8, 1993

The Honorable John D. Rockefeller IV
Chairman
Senate Veterans' Affairs Committee
414 Russell Senate Building
Washington, DC 20510

Dear Mr. Chairman:

Due to a long-standing, previous commitment, I will be out of town on October 21 and, therefore, unable to attend the hearings on the National Academy of Sciences (Institute of Medicine) Report, *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*. I submit herewith my written testimony. The following two suggestions are in addition to or included with those recommendations provided to the Department of Veterans Affairs Review Panel in my letter of August 27 (attached).

Immune System and All Cancers Combined

The Institute of Medicine Report fails to include any conclusions regarding the ability of dioxin to cause or be associated with an overall increase in the cancer rate (pages 8-12). The Environmental Protection Agency (EPA) recently reviewed the same studies on chemical production workers summarized by the IOM and came to a definite conclusion, as part of its ongoing effort to evaluate the risks of dioxin. After undergoing extensive public and expert review, and after open workshop meetings, the EPA's second draft report on human epidemiology (EPA Publication No. EPA/600/AP-92/001g, June, 1993, page 7-71) states:

> *Other TCDD related hormonal effects, including immune suppression, may result in multi-organ sensitivity and may contribute to the overall increased mortality from all malignancies combined seen in all four cohort production worker subcohorts with higher estimated TCDD exposures...These increased relative risks, while not large (10% to 70%) are consistent and are either statistically significant or of borderline significance. While no one tissue site can account for this observed increase, lung cancer is also increased in three of these.*

In view of this fact, I strongly recommend that the Senate Veterans' Affairs Committee amend existing legislation to authorize compensation to Vietnam veterans experiencing any form of cancer or to their families in the case of deceased Vietnam veterans.

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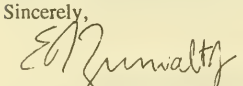
Birth Defects

The issue of the possible health effects on the children of Vietnam veterans was left unresolved by the National Academy of Sciences' review because the Committee did not find enough studies of sufficient size on the reproductive effects of Agent Orange. The studies that were reviewed did not address the pattern of disability that is being reported most frequently in the children of Vietnam veterans. This pattern was defined through a report to the NAS from the Association of Birth Defect Children and the New Jersey Agent Orange Commission. These two agencies have been collecting national data on the disabilities in the children of Vietnam veterans and comparing these data to children with disabilities whose fathers are non-veterans. They are looking specifically at learning and attention problems, chronic skin disorders, allergic problems, growth hormone deficiency, chronic infections, emotional / behavioral difficulties, prolapsed heart valves and a range of symptoms that may be related to dysfunctional immune systems.

The EPA draft chapter on human epidemiology concluded that there is an association between male reproductive hormones and serum dioxin levels (page 7-161). Furthermore, a study published by Dr. Arnold Schecter in *Chemosphere* has confirmed that dioxin can be found in the seminal fluid of Vietnam veterans even twenty years after their exposure to Agent Orange in Vietnam.

The NAS Committee recommends in their report that a study consisting of 9,000 Vietnam veterans' children and 9,000 non-veterans' children would be required to resolve the issue of reproductive effects of Agent Orange. I ask this committee to consider immediate funding of such a study. I strongly recommend continuation of this effort through the registry developed by the Association of Birth Defect Children and the New Jersey Agent Orange Commission since this project has already been developed and tested for more than a year.

Sincerely,



Admiral E.R. Zumwalt, Jr., USN (Ret.)
Chairman, Agent Orange Coordinating Council

1500 Wilson Blvd., Suite 641
Arlington, VA 22209
703/527-5380

c: The Honorable Tom Daschle
Mr. Jim Gottlieb

E. R. ZUMWALT, JR.
ADMIRAL, U. S. NAVY (RET.)

August 27, 1993

Dr. Susan H. Mather, Chair
NAS Agent Orange Report Review Panel
ACMD for Environmental Medicine and
Public Health
Department of Veterans Affairs
801 I Street NW
Washington, DC 20001

Dear Dr. Mather:

On behalf of the Agent Orange Coordinating Council, the membership of which is attached, I make the following recommendations concerning the actions, which in our judgment, Secretary Brown should take in responding to the findings of the Institute of Medicine's Agent Orange Report. These are designed to build on the momentum achieved by Secretary Brown's prompt implementation of the findings of the NAS panel concerning Hodgkin's disease and porphyria cutanea tarda (PCT):

1. Immediately authorize compensation for Agent Orange exposed veterans (and/or their families) who suffer from the three categories of disease for which the panel found "limited / suggestive evidence," namely respiratory cancers, prostate cancer and multiple myeloma. These diseases appear to us to fall within the clear language and intent of the law which merely requires that evidence be "as likely as not."

2. Initiate a more detailed review immediately to establish the reasonability of authorizing compensation for "all cancers" since increases in all types of cancer have been determined to occur in various studies. This recommendation is supported by EPA's conclusions in its second draft on human epidemiology that dioxin causes statistically significant or borderline statistically significant increases in all cancers, due to its effects on the immune system or hormonal change.

   In connection with this review, the group established to do the analysis should be required to be guided by the analysis supplied to the VA General Counsel Mary Lou Keener on August 24 by Mark Venuti of the National Veterans Legal Services Project (NVLSP) so that the requirements of the law and the discretion conferred by the law upon the Secretary are properly linked with the NAS report.

3. Initiate a careful review of the past performance of senior career VA officials who have continued to maintain the position that there must be a clear cause and effect relationship between exposure and disease prior to authorizing compensation. As a member of the Committee on Environmental Hazards until its disestablishment by Congress, I became personally convinced that despite the Nehmer litigation and the clear language and obvious intent of P.L. 102-4, there

are clearly personnel in the Department of Veterans Affairs who continue to work for maintaining a cause and effect test.

This has resulted in years of delay in providing essential justice to Vietnam veterans suffering from the effects of exposure to Agent Orange. The egregious harm that has been done makes it important that such a review be carried out now that the NAS panel has so clearly established what these career personnel have sought to avoid.

4. Retain the previous decision to authorize compensation for Vietnam veterans suffering peripheral neuropathy. The very small number affected and the fact that a previous affirmative decision has been announced make this an imperative.

5. Initiate one or more major epidemiological studies designed to resolve the remaining concerns of Vietnam veterans and their survivors with reproductive problems, birth defects and all of the diseases reported by NAS as having "inadequate or insufficient evidence" to determine whether an association exists, including those for which the panel decided there was "limited or suggestive evidence" of no association.

6. Establish an independent, non-governmental panel to review and approve a new, expanded research protocol for both the Ranch Hand cohort and the Army Chemical Corps cohort as recommended by the NAS panel.

7. Concur with the NAS panel's recommendation that the use of biomarkers, especially TCDD, be further developed but declare that such markers must not be regarded as exposure surrogates to the exclusion of other sources of exposure information.

8. Establish a non-governmental organization with appropriate experience in historical exposure reconstruction to develop and test models of herbicide exposure for use in studies of Vietnam veterans as recommended by the NAS panel. However, instruct this panel to begin their work by examining the use of the previously manipulated but available data in CDC studies. Good data exists and some of the manipulated data can be reconstructed to provide objective results.

9. Establish an independent, non-governmental scientific panel to evaluate the exposure reconstruction models developed.

10. If the scientific panel established pursuant to the recommendation above determines that a valid exposure reconstruction model is feasible, facilitate additional epidemiological studies of veterans.

Sincerely,

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